STUDY OF CEREBRAL BLOOD FLOW IN INSULIN DEPENDENT DIABETIC PATIENTS

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Presented By

Hesham Ramadan Abdel-Gawad Khater
M.B.B. Ch, Ain Shams University (1988)
M.Sc. of Pediatrics, Ain Shams University (1995)

Supervisors

Prof. Dr.
MONA ABDEL KADER SALEM
Professor of Pediatrics
Faculty of Medicine,
Ain Shams University

Prof. Dr.
TAREEF HAMZA SALLAM
Professor of Clinical Pathology
Faculty of Medicine,
Ain Shams University

Prof. Dr. MOHAMMAD OSSAMA ABDUL-GHANI
Professor of Neurology
Faculty of Medicine, Ain Shams University

Dr. NAGHAM MOHAMMAD SAMI EL BEBLAWI
Lecturer of Pediatrics
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University

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List of Abbreviations

Abs	= Absorbance.
ACA	= Anterior Cerebral Artery
ACZ	= Acetazolamide.
AER	= Albumin exertion rate
AGE	= Advanced glycation end products.
AGE-LDL	= Advanced glycation end products-Low density lipoproteins.
BMI	= Body mass index.
CBF	= Cerebral blood flow.
CCA	= Common Carotid Artery
CHD	= Coronary heart disease.
CNS	= Central Nervaus System
CO_2	= Carbon dioxide
CPB	= Cardiopulmonary by pass
CS	= Carotid Siphon.
DKA	= Diabetic ketoacidosis
DM	= Diabetes Mellitus
DPT-1	= Diabetes Prevention Trial.
EEG	= Electro-Encephalogram.
ENDIT	= European Nicotinamide Diabetes Intervention Trial.
ESRD	= End stage renal disease
GAD	= Glutamic acid decarboxylase

GDM	= Gestional Diabetes Mellitus.
Hb	= Hemoglobin
HbA1c	= Glycated hemoglobin
Hct%	= Hematocrit%
HDL	= High density lipoproteins
HDL-C	= High density-lipoprotein-cholesterol.
IAA	= Insulin auto-antibodies
ICA	= Islet cell antibody
IDDM	= Insulin Dependent Diabetes Mellitus.
IDL	= Intermediate density lipoproteins
IFG	= Impaired fasting glycemia
IGT	= Impaired glucose tolerance
JDF	= Juvenile Diabetes Foundation
LDL-C	= Low density lipoprotein-cholesterol
MCA	= Middle Cerebral Artery
MFVs of MCAs	= Mean flow velocities of Middle Cerebral Arteries.
MHC	= Major histo-compatibility complex
MHz	= Miga Hertz.
MODY	= Maturity onset diabetes of the young.
NAD	= Nicotinic adeninine dinucleotide.
NIDDM	= Non Insulin Dependent Diabetes Mellitus.
NO	= Nitric Oxide
NOD mice	= Non obese diabetic mice
O_2	= Oxygen

PCAs	= Posterior Cerebral Arteries
PET	= Positron emission tomography.
Plt	= Platelets
RBCs Deform	= Red blood cells deformability
rCBF	= Regional cerebral blood flow.
rCBFV	= Regional cerebral blood flow volume.
SPECT	= Single photon emission computarized tomography
TC	= Total cholesterol
TCD	= Transcranial doppler sonography
TG	= Triglycerides
TF	= Total fraction
TLC	= Total leukocytic count
VLDL	= Very low density lipoproteins
VM R	= Vasomotor reactivity
WHO	= World Health Organization
Xe^{133}	= $Xenon^{133}$

Introduction and Aim of the work

INTRODUCTION

Diabetes mellitus is a medical syndrome with unifying common features of hyperglycemia (**Malone, 1994**).

Insulin dependent diabetes mellitus is the most common form of diabetes that occurs in children. Insulin dependency implies that administration of insulin is essential to prevent spontaneous ketosis. (**Fajans, 1990**).

Haemorheologic abnormalities have been reported in diabetes mellitus, they may play an important role in the pathogenesis of vascular complications (**Lechner et al., 1986** and **Cathy and Hegason 1988**). The influence of altered haemorheology on the cerebral blood flow has been suggested (**Abdel Ghani 1986** and **Harmsen et al., 1990**).

Recently, transcutneous doppler ultrasound has been used to study the cerebral circulation in human adults and newborns by determining changes in blood velocity. The advantages of this technique are that it is non-invasive and provides valuable information. (**Adams et al., 1992**).

Also transcranial doppler ultrasonography was used and applied to evaluate the cerebral blood flow and cerebrovascular reactivity using Acetazalomide (Diamox) IV in type-1 diabetics as **Fulsedi et al. (1997)** reported that cerebrovascular reactivity is impaired in type-1 diabetics with a disease duration more than 10 years.

AIM OF THE WORK

The aim of this study is to assess the role of transcranial doppler ultransonography-Acetazolamide test in the measure-ment of cerebral blood flow velocity and cerebrovascular reactivity in type-1 diabetes and to evaluate the changes in different rheological parameters (plasma viscosity, RBCs deformability and fibrinogen) and changes in lipid profile and their impact on the cerebral blood flow and cerebraovascular reactivity.

Review of Literature

Diabetes Mellitus

It is a syndrome of disturbed energy homeostasis caused by deficiency of insulin or its action and resulting in abnormal metabolism of carbohydrate, protein and fat. It is the most common endocrine metabolic disorder of childhood and adolescence with important consequences on physical and emotional development **(Sperling, 1996)**.

Also, DM can be defined as a heterogeneous primary disorder of carbohydrate metabolism with multiple etiologic factors that generally involve absolute or relative insulin deficiency or insulin resistance or both. All causes of diabetes ultimately lead to hyperglycemia which is the hallmark of this syndrome **(Olfsky, 1992)**.

The major metabolic complications associated with insulin dependent diabetes mellitus are the development of diabetic keto-acidosis and hypoglycemia **(Salem et al.,1989a)**.

Classification of Diabetes Mellitus

The first widely accepted classification of diabetes mellitus was published by World Health Organization (WHO) in 1980, and in modified form in 1985.

The 1980 and 1985 classifications of diabetes mellitus and allied categories of glucose intolerance included clinical classes and two statistical risk classes. The 1980 expert committee proposed two major classes of diabetes mellitus and named them Insulin dependent diabetes mellitus (IDDM) or type-1, and Non-Insulin dependent diabetes mellitus (NIDDM) or type-2.

In the 1985 study group report, a new class of malnutrition-related diabetes mellitus (MRDM) was introduced. In both the 1980 and 1985 reports other classes of diabetes included other types of diabetes mellitus related to certain conditions and syndromes of impaired glucose tolerance (IGT).

In 1998, WHO proposed a new classification of Diabetes Mellitus (DM) which encompass both clinical stages and etiological types of diabetes mellitus and other categories of hyperglycemia **(Kuzuga and Matsuda, 1998).** Tables (1&2) and figure (1).

The main changes proposed are as follows:

- Diagnostic fasting plasma (Blood) glucose value has bean lowered to ≥ 7.0 mmol /L.
- Impaired glucose tolerance is changed to allow for the new fasting level.
- A new category of impaired fasting Glycemia (IFG) is proposed to encompass values which are above normal of fasting blood glucose but below diagnostic cut off for diabetes (plasma ≥ 6.1 to < 7.0 mmol / L, whole blood ≥ 5.6 to < 6.1mmol L /L).
- Gestational Diabetes Mellitus (GDM) now includes gestational impaired glucose tolerance as well as the GDM.

The new classification has several applications, it contains stages which reflects the various degrees of hyperglycemia in individual subjects with any of the disease processes which may lead to diabetes mellitus.

All subjects with diabetes mellitus can be categorized according to clinical stage and this is achievable in all circumstances. A disease process may be present but may not have progressed far enough to cause hyperglycemia. The etiological classification reflects the fact that, the defect or process which may lead to diabetes mellitus may be identifiable at any stage in the development of diabetes, even at the stage of normoglycemia.

Table (1) : Etiological classification of disorders of glycemia:

- **Type-1** (beta- cell destruction, usually lead to absolute insulin deficiency)
  - Autoimmune.
  - Idiopathic.

- **Types-2** (May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance).

- **Other specific types** (see table 2)
  - Genetic defects of beta-cell function.
  - Genetic defects in insulin action.
  - Diseases of the exocrine pancreas.
  - Endocrinopathies.
  - Drug or chemical induced.
  - Infections.
  - Uncommon forms of immune-mediated diabetes.
  - Other genetic syndromes sometimes associated with diabetes.
- **Gestional Diabetes Mellitus**

(Alberti and Zimmet, 1998)

Table (2): Other specific types of diabetes:

- **Genetic defects of beta-cell function**
  - Chromosome 20, HN F4α (MODY1)
  - Chromosome 7, glucokinase (MODY2)
  - Chromosome 12, HN FIα (MODY3)
  - Chromosome 13, IPF-1 (MODY4)
  - Mitochondrial DNA 3243 mutation - Others
- **Genetic defects in insulin action:**
  - Type-A insulin resistance
  - Leprechaunism - Rabson- Mendenhall sysndrome
  - Lipoatrophic diabetes - Others
- **Diseases of the exocrine pancreas**
  - Fibrocalculus pancreatopathy
  - Pancreatitis - Trauma - Pancreatectomy
  - Neoplasia
  - Cystic fibrosis - Hemochromatosis - Others
- **Endocrinopathies**
  - Cushing syndrome - Acromegaly
  - Pheochromocytoma
  - Glucagonema - Hyperthyroidism -Somatostatinoma
  - Others
- **Drug or chemical induced**
- **Infections**
  - Congenital rubella. – Cytomegalovirus. - Others.
- **Uncommon forms of immune-mediated diabetes:**
  - Insulin immune syndrome (antibodies to insulin)
  - Anti-insulin receptor antibodies
  - "Stiffman" syndrome - Others
- **Other genetic –syndromes:**

(Alberti and Zimmet, 1998)

Figure (1): Shows disorders of glycemia:

etiological types and clinical stages.

Stages / Types	Normoglycemia	Hyperglycemia			
	Normal glucose Tolerance	IGT and /or IFG	Diabetes Mellitus		
			Not insulin requiring	Insulin requiring for control	Insulin requiring for survival
Type-1 -Autoimmune -Idiopathic	←——	——	——	——	——→
Type-2 Predominantly insulin resistance -Predominantly insulin secretory defects	←——	——	——→	- - -	- - -→
Other specific types	←——	——	——→	- - -	- - -→
Gestational diabetes	←——	——	——→	- - -	- - -→

IFG = Impaired fasting glycemia

IGT = Impaired glucose tolerance

(Alberti and Zimmet, 1998)

Type-1 Diabetes Mellitus

IDDM is the most common endocrine metabolic disorder of child- hood, and adolescence **(Sperling, 1990).** It is a serious health problem being the 3rd greatest cause of death throughout the world, and if not treated, it is responsible for many complications, affecting various systems in the body **(Kaufman, 1998).**

It is a catabolic disorder in which circulating insulin is virtually absent, plasma glucagon is elevated, and the pancreatic B-cells fail to respond to all insulinogenic stimuli.

Exogenous insulin is therefore required to reverse the catabolic state, prevent ketosis, reduce the hyperglucagonemia, and bring the elevated blood glucose level down **(Karam, 1988).**

Incidence and Prevalence:

The prevalence of IDDM shows marked geographical variation, spanning a wide spectrum from Finland, where it is the commonest to Japan, where the frequency is less than one-thirtieth of that in Finland. There is some evidence that the incidence of IDDM in childhood is increasing in some areas, perhaps as much as two folds each decade **(Stewart –Brown et al., 1983).**

This increase may be related to relative affluence, as IDDM seems to be associated with the higher socio-economic classes **(Ardon et al., 1987).**

Intercurrent infections could also explain the seasonal variation in the presentation of IDDM, which occurs much more commonly in the autumn and winter, when viral and other infections are more prevalent **(Atkinson and Maclaren, 1994).**

IDDM presents most commonly in children and adolescents; the peak age of onset is 11-13 years. However, it can appear at any age and a significant proportion of newly presenting elderly diabetic patients up to 10% of those over 65 years of age will go on to require insulin. For this reason alone, the outmoded term Juvenile-onset diabetes, should be abandoned **(Bates, 1986).**

Interestingly, up to 20% of patients with apparently typical NIDDM display evidence of auto-immune activity directed against the B-cells, suggesting that they may suffer from a particularly slowly evolving variant of insulin-dependent diabetes mellitus **(Rowky et al., 1992).**

Pathogenesis of Type-1 Diabetes Mellitus :

A- Genetic Factors: The etiology of IDDM is multi-factorial, complex and still imperfectly understood. IDDM is the result of an

unfavorable interaction between environmental factors and an inherited predisposition to the disease. Studies in monozygotic twins suggest that the genetic component accounts for 30-40% of the total risk of developing IDDM **(Atkinson and Maclaren, 1994).**

A new approach to the genetics of diabetes was provided by the observed association of IDDM with certain HLA antigens **(Todd et al., 1988).**

Inheritance of susceptibility to IDDM does not depend on a single gene, but is determined by several genes at different loci. The most important appears to reside in the HLA major histocompitability complex (MHC) class II region on the short arm of chromosome G6 and has been designated IDDM **(Atkinson and Maclaren, 1994).**

This locus probably accounts for most of the genetic susceptibility and explains the long recognized association of IDDM with HLA-DR_3 and HLA-DR_4 serotypes; recent detailed studies of the gene sequences themselves suggest that these associations can be explained by polymorphisms in specific peptide subunits **(The DQB chain)** of the glycoproteins that constitute the HLA antigens. Other susceptibility genes of lesser importance include the region of the insulin gene itself on the short arm of

chromosome-II ($IDDM_2$) and a region on the long arm of chromosome -2 **(2 q^{32}; $IDDM_3$) (Davies et al., 1994).**

These findings provide a rational framework for the genetic factors associated with type-1 diabetes as suggested by the increased incidence in some families, the concordance rates in monozygotic twins and the ethnic and racial differences in incidence. Although these recent genetic findings suggest that different genes on chromosome number 6 confer susceptibility to diabetes, factors other than pure inheritance are involved in producing clinical disease, thus the concordance rate among identical twins one of them has IDDM is at most only 50 per cent, suggesting the participation of an environmental triggering factor **(Sperling, 1990).**

In type-1 diabetes, the inheritance of HLA-DR_3 or DR_4 appears to confer a two or three folds greater relative risk for developing IDDM. When both DR_3 and DR_4 are inherited together however, the relative risk for developing diabetes is 7 to 10 folds greater, suggesting that DR_3 and DR_4 are additive in their effect of conferring relative risk **(Todd et al., 1988).**

A rare genetic type of properdin factor B (BF^{F1}) known to be closely linked to the HLA system on chromosome 6 was found in over 20 percent of type-1 diabetics but in only 2 percent of healthy

subjects, yielding relative risk of 15 folds for those who inherit this genetic marker **(Sperling, 1990).**

B-Environmental Factors:

Sperling. (1997) Said that the most likely factors are viruses and diet. Certain viruses are known to be pancreotropic among them mumps, coxsackie B_4 and other enteroviruses.

Cavallo et al. (1992) found that mumps infection of a human B-cell (insulinoma) line in vitro induced the release of interlukins 1 and 6 and also up regulated the expression of HLA class I and II.

Salem et al. (1993) demonstrated higher prevalence of mumps virus antibodies in sera of IDDM patients compared to control groups. These findings agree with other investigations **(Shaker et al., 1984)** and they suggested that mumps virus might be an important infectious agent in the development of IDDM in Egypt. Moreover, 20% of subjects affected by congenital rubella develop diabetes during childhood **(Bingley and Gale, 1993).**

In 1994, **Yoon and Kominek** said that coxsackie B viruses are involved in the etiology of IDDM as several epidemiological studies have reported high frequency of Ig-M anti- coxsackie- B antibodies, in newly diagnosed children with IDDM.

Hao et al. (1993) found that endogenous retroviruses have also been implicated in humans. Anti-insulin auto-antibodies from IDDM patients and their non-diabetic, first degree relatives have been found to cross react with the retroviral P 73 antigen in up to 75% of cases, where as only 3% of non-diabetic unrelated controls have P-73 binding antibodies.

Fohlman and Friman. (1993) claimed that other viruses like coxsackie- A and Echo viruses, hepatitis- A virus, varicella zoster, measles, polio and influenza may be associated with IDDM in humans.

Farrel and Keeffe. (1998) demonstrated that IDDM has developed in association with hepatitis-A infection.

C-Role of Autoimmunity:

Type-1 diabetes mellitus is an autoimmune disease **(Styne, 1994)**. The evidence of an autoimmune etiology for type-1 diabetes mellitus dates from as early as 1910 with the description of round cell infiltration of the pancreas **(Gepts and Lecompt, 1981)**.

Its histological hallmark is "insulinitis", mononuclear infiltration of pancreatic islets leading to specific destruction of

pancreatic beta cells **(Tenkins, 1994)**. The autoimmune destruction of beta islet cells of the pancreas has been going on for months or years before clinical syndromes emerge **(Tarn, 1988).**

Cytoplasmic islet cell antibodies (ICA) are detected by indirect immuno-fluorescence on unfixed human pancreas and are now measured in standardized international JDF **(Juvenile Diabetes Foundation)** units, the antigen against which ICA are directed is unknown, but it may be an islet ganglioside.

ICA are present in about 80% of children at diagnosis and have been detected up to 15 years before diagnosis of IDDM. Other antibodies: insulin auto-antibodies and antibodies against a 64 KD islet antigen (recently identified as glutamic acid decarboxylase-GAD) have also been described **(Zimmet, 1993).**

In a study done by **Dittler et al. (1998)** to assess the sensitivity and predictive value of the glutamic acid decarboxylase (GAD)- tyrosine phosphatase IA-2 combination (combi) test in first degree relatives of type-1 diabetic patients compared with islet cell antibody (ICA) and insulin auto-antibodies (IAA). The results indicated that the GAD-IA-2 combi test is a valuable marker for first-line screening and risk assessments of type-1 diabetes in relatives.

Salem et al. (1998) proved that anti-GAD could be considered an important predictor of type-1 diabetes and estimation of its level could be a part of screening for new cases.

In auto-immune diseases, the normal state of self-tolerance is disturbed; "self" becomes recognized as " non-self" and tissue destruction results. The mechanism of this is unclear. A new antigen may appear on the cell surface, perhaps as a result of viral infection or aberrant expression on the cell surface of an antigen that is normally sequestrated. If this is present in association with major histocompatibility complex (MHC) class 2 antigens, T-lymphocytes could be activated. Once the auto-immune process has been initiated, beta cell destruction probably results from antigen specific attack by cytotoxic T-lymphocytes, possibly supplemented by cytokine release by macrophages and natural killer cells **(Zimmet, 1993)**.

Salem et al. (1989-b) found that age, seasonal variation, viral infections, emotional stress, multiparty, high birth order and consanguinity between parents and family history of diabetes are risk factors in the development of IDDM.

Complications of Type-1 Diabetes Mellitus

Early Complications:

I-Hypoglycemia **II- Diabetic Ketoacidosis**

I-Hypoglycemia

The problem of hypoglycemia is common in insulin dependent diabetics, particularly when aggressive efforts are made to keep both the fasting and post-prandial plasma glucose within the normal range. Hypoglycemia may be caused by missing a meal or doing unexpected exercise but can occur in the absence of known precipitating events **(Foster, 1987).** Daytime episodes of hypoglycemia are usually recognized by adrenergic symptoms, such as sweating, nervousness, tremors and hunger. Also neuroglycopenic symptoms that include blurred or double vision, headache, lethargy, clumpsy, confusion, convulsions and coma **(Habel, 1993).**

Hypoglycemia during sleep may produce no symptoms or cause night sweats, unpleasant dreams and early morning headache **(Foster, 1987).**

Acute hypoglycemia causes major adaptive responses in the brain and neuroendocrine function which include an increase in cerebral blood flow and concerted counter-regulatory hormonal

responses that restore normoglycemia. Cognitive function is rapidly and profoundly affected by neuroglycopenia. This stage usually follows the onset of hypoglycemic symptoms and signs, but the latter may be insignificant or absent altogether (hypoglycemia unawareness) in some diabetic patients, especially those with long standing IDDM or recurrent hypoglycemia **(Neil et al., 1987).**

Most of the features of acute hypoglycemia are rapidly reversed by raising the blood glucose concentration, but severe and prolonged hypoglycemia may cause permanent neurological damage which is focused on specific brain regions, notably the hippo campus, cortex and caudate nucleus **(Patrick and Compell, 1990).**

Chronic or recurrent hypoglycemia has several consequences in the CNS, including loss of awareness of hypoglycemia and effects on higher functions. Hypoglycemia unawareness affects up to 30% of patients with longstanding IDDM, and may also be induced by strict glycemic control and recurrent hypoglycemia; in the latter cases, it may be partially restored by allowing overall blood glucose levels to rise and, above all, by avoiding hypoglycemic episodes **(Kumagai et al., 1995).**

With the current derive towards strict diabetic control and the inevitably increased frequency and severity of hypoglycemia

that this will bring, concern has bean expressed over the possible neurological effects of repeated mild to moderate hypoglycemia. There is some evidence that this may cause cumulative intellectual impairment, which in some cases may be severe enough to interfere with intellectually demanding Jobs **(Hopkins and Williams, 1994).**

Auer and Siesjo. (1993) stated that with prolonged and profound hypoglycemia, permanent neurological deficit and death may result.

II-Diabetic Ketoacidosis

Diabetic ketoacidosis is the most important complication of diabetes in childhood. It has a high mortality in spite of the improvement in its management, accounting for over half of all deaths in diabetic patients under the age of 34 years **(Ghaly et al., 1991).**

Insulin deficiency is the major endocrine abnormality responsible for the metabolic changes of DKA, although counter regulatory hormones activity is important in applying the consequences of insulin deficiency So, absence of adequate blood level of insulin alone will produce hyperglycemia and ketosis but generally will not precipitate DKA. There must be both a relative lack of insulin and relative over activity of the counter regulatory hormones to cause DKA **(Krane, 1987).**

Chronic or Late Diabetic Complications

Chronic Diabetic Complications Include:

- Microangiopathy (nephropathy, retinopathy and neuropathy).
- Macrovascular (Cardiovascular, Cerebrovascular and peripheral vascular disease).
- Growth disturbances.
- Joint dysfunction
- Autoimmune disease
- Muriac syndrome.

(Plotinick, 1994).

Risk Factors For The Development of Diabetic Complications:

- Blood glucose control
- Smoking
- Genetic components
- Blood pressure
- Blood lipids (Cholesterol and Triglycerides)
- Protein intake
- Circulating levels of insulin, proinsulin or insulin split products
- Metabolic or hormonal milieu of puberty **(White, 1996).**

Diabetic Retinopathy:

As with all diabetic complications, the development of retinopathy depends on the duration of the disease **(Nathan, 1993).** Retinopathy is the most common chronic complication of IDDM **(Sjolie et al., 1997).** Essentially every diabetic will develop

background retinopathy once they have had diabetes for 20 years **(Taylor, 1997)**.

Blindness is one of the most feared complications. It is either due to a specific retinopathy causing hemorrhage, maculopathy, cataract formation, or most rarely due to rubetic glucoma **(Watkins et al., 1996)**.

It passes into three stages, the first stage consists of early changes before the onset of proliferative retinopathy. Cellular and haemodynamic alterations may be present **(Bursell et al., 1995)**.

As, the disease progresses, the clinically evident signs of early or non- proliferative diabetic retinopathy appear. The classic signs are retinal micro-aneurysms, small dots and bloot retinal hemorrhages, cotton wall spots, venous loops, venous caliber changes and retinal capillary dropout **(Aiello et al., 1994)**.

The more advanced stage of diabetic retinopathy is proliferative diabetic retinopathy. During this stage, active proliferation of new vessels occurs on the retinal surface. In severe cases, proliferation of new vessels may occur on both the iris and anterior chamber angle and may obstruct the aqueous fluid outflow leading to neovascular glucoma, much feared and severe sight-threatening disorder **(Feke et al., 1994)**.

Diabetic Nephropathy:

In 1995, according to registries of end-stage renal disease (ESRD) in the United States, diabetes mellitus was the leading cause of renal failure worldwide **(Friedman, 1996)**.

A strong familial predisposition to kidney disease in diabetes is evident. Cardiovascular disease and cardiovascular death are more prevalent in patients with IDDM who have nephropathy **(Earle et al., 1992)**. Besides the genetic factor, the pathogenesis of diabetic nephropathy includes other factors such as metabolic control **(Barnas et al., 1997)**. Hypertension, disturbed lipid and lipoprotein pattern contribute to the onset of micro-albuminuria **(Rudberg et al., 1997)**, and increased glomerular filtration rate related to the associated intraglomerular hypertension **(Pecis et al., 1997)**.

Early morphologic changes in the diabetic kidney include thickening of the glomerular basement membrane as well as tubular basement membrane and Bowmans' capsule. Increased mesangium and glomerular basement membrane contain increased amounts of type IV and VI collagen, laminan and fibronectin. Mesangial expansion ultimately restricts glomerular capillary luminal volume, distorts glomerular capillary diameter and length relationships and diminished filtration surface. All of the major manifestations of

clinical diabetic nephropathy can be related to mesangial expansion **(Mogenson et al., 1993)**.

Diabetic nephropathy may be functionally silent for long periods (10-15 years). Recently, it has been suggested that proteinuria is not simply a marker of the extent of glomerular damage, but proteinuria per se, may contribute to glomerular damage **(Mathiesen et al., 1997).**

Microalbuminuria signifies glomerular basement and mesangial expansion **(Fioretto et al., 1994)**. The recent introduction of assays for micro-albuminuria as albumin excretion rate (AER) of 30-300 mg/24 hours has allowed early identification of individuals at risk of nephropathy **(Zimmet, 1993)**.

In IDDM, clinical proteinuria (AER > 300 mg / 24 hours) takes 10-20 years to develop. Once fixed proteinuria is established, the prognosis is especially poor; only 28% survive after 10 years **(Zimmet, 1993).**

Abdel Rassoul. (1993) proved that micro-albuminuria, the marker of the incipient stage of diabetic nephropathy is absent in the 1st 5 years of IDDM, while it affects 13.6% of IDDM children with a disease duration more than 5 years. Bad metabolic control

and modest elevations of blood pressure are features of micro-albuminuric patients.

It is generally believed that DM predisposes to infections of the urinary tract and the incidence of bacteremia was significantly increased with increased duration of diabetes **(Salem and Mira, 1990).**

Diabetic- Neuropathy:

The incidence of diabetic neuropathy shows a wide variability depending on the diagnostic criteria used. Epidemiological studies measuring muscular weakness, pain and loss of sensation show a 40% incidence of neuropathy, however if one looks at reduced nerve conduction even in the absence of clinical signs, the incidence increases considerably (**Combi et al., 1987**).

There are three recognized forms of diabetic neuropathy: mono-neuropathy involving a peripheral or cranial nerve, symmetrical peripheral polyneuropathy (the most common), and autonomic neuropathy **(Vinik and Mitchell, 1988).** The last two are considered to be metabolic in etiology, where as mono-neuropathy is usually attributed to disease of vasa nervosum (**Greene et al., 1988**).

- **Mono-neuropathy:**

Diabetic mono-neuropathy may involve the femoral, obturator, siatic, median, or ulnar nerve or may affect a cranial nerve in isolation. The usual picture is the sudden appearance of wrist drop, foot drop, or paralysis of the third, fourth, or sixth cranial nerve. Several nerves may be involved at the same time (mono neuritis multiplex), but this is unusual **(Vinik and Mitchell, 1988)**.

- **Symmetrical Peripheral Polyneuropathy:**

The most common manifestation of the peripheral neuropathy of diabetes is symmetrical sensory loss in the distal extremities **(Vinik and Mitchell, 1988)**. Motor deficits are less common, although the Achilles reflex is frequently absent, sometimes even at the time of diagnosis of diabetes.

The most common symptoms are numbness, tingling, and burning that is worse at night. Lancinating or lighning pain (tabes – like) may become extremely severe, and suicides are known to have occurred because of it. Such patients should be advised that their pain is not permanent and will subside spontaneously within months to years as the involved neurons become destroyed. **(Unger and Foster, 1992)**.

Salem et al. (1987) reported that 30% of asymptomatic diabetic patients had abnormal motor nerve conduction. The

diminished sensory perception of diabetic neuropathy, even when asymptomatic may lead to unperceived injuries to the skin and Joints, causing calluses, ulceration and neuropathic atrophy (Charcot Joints). Painless tarsal and leg fractures may occur, especially in those who walk or Jog for exercise **(Unger and Foster, 1992).**

It is recommended that nerve function studies must be done at intervals of six months in order to detect any changes. There is a good evidence that improvement in blood glucose control could prevent and even reverse neuro-physiological changes **(Salem et al., 1987).**

- **Autonomic Neuropathy:**

The manifestations of autonomic neuropathy include anhidrosis of the lower extremities (sometimes associated with hyperhydrosis of the upper half of the body), orthostatic hypotension, and motility disturbances of the bladder, oesophagus, stomach, gall bladder, small intestine and colon **(Hilsted, 1982).**

The syndrome of counter-regulatory failure leading to hypoglycemia may also be related to autonomic neuropathy, the normal fluctuations in pupil size, known as pupillary unrest, are reduced by about 35% in diabetic patients of age 25 to 43 years **(Hreidarson and Gundersen, 1988).**

The ability to maintain meiosis in a continuos light is also impaired **(Unger and Foster, 1992)**. The most serious consequence of autonomic neuropathy is an alteration in cardic sympathetic innervation with Q-T interval prolongation, which can be associated with sudden arrhythmia and death **(Kahn et al., 1987).**

Cerebral Complications of Diabetes Mellitus

Peripheral neuropathy is a well-known complication of diabetes mellitus. In recent years, evidence is emerging that diabetes also affects the central nervous system **(Biessels et al., 1994)**.

Both acute and chronic metabolic and vascular disturbances can impair the function and structural integrity of the brain in diabetic patients. For example, diabetes increases the risk for stroke **(Abbott et al., 1987)** and stroke outcome is worse in diabetic patients **(Bell, 1994)**. In addition, hyperglycemic and hypoglycemic episodes may result in acute cerebral dysfunction **(Cryer et al., 1994)**.

Neuro-psychological studies in diabetic patients have reported variable performance deficits on a wide range of cognitive tests. Problems with learning and memory, problem solving and mental and motor speed have been noted. The nature and severity of cognitive deficits in diabetic patients appear to be dependent on age, possibly also on the type of diabetes (insulin dependent diabetes versus non-insulin dependent diabetes). **(Tun et al., 1990)**.

In diabetic children, age at diabetes onset and hypoglycemic episodes appear to be the prime determinants of cognitive changes; children and adolescents who develop diabetes before five years of age **(Rovet et al., 1987)** and children who frequently experience hypoglycemic episodes **(Rovet and Alvarez, 1997)** are more likely to express cognitive deficits. **Salem et al. (1999)** in their study on diabetic children, they revealed lower I.Q scores and level of school achievement in children below 5 years at the onset of diabetes that could be explained by the possibility that young children have a critical period of brain development in which hypoglycemia may have a greater long term effect on cerebral function of developing brain. Young children may have disproportionately high brain requirement for glucose and hence more liable to hypoglycemia **(Service, 1995).**

Visual and spatial abilities may even be affected by asymptomatic recurrent hypoglycemia **(Golden et al., 1989).** Disease duration and poor glycemic control as determined by HbA1c values may be additional factors influencing cognitive functions in diabetic children. In adult insulin-dependent-diabetes mellitus patients, small but detectable reductions in mental efficiency have been reported repeatedly **(Ryan et al., 1992).**

Severe deficits occur only in few patients, the pattern of impairment across different cognitive tasks tends to vary among

studies. This variation might be due to the relatively subtle nature of the cognitive deficits, as well as the heterogeneity of study populations. In addition, exposure to different risk factors such as frequent hypoglycemic episodes, on the one hand, and chronic hyperglycemia on the other hand, may vary between patients **(Richardson, 1990)**.

Glycemic control plays a role in the prevention of cerebral complications in IDDM patients. On the other hand, poor glycemic control as reflected by increased HbA1c values are associated with cognitive dysfunction **(Ryan and Williams, 1993).** Moreover, the development of other complications associated with poor glycemic control, such as peripheral neuropathy is associated with cognitive dysfunction. On the other hand, intensive treatment increases the frequency of hypoglycemic episodes and may thus adversely affect the brain **(Ryan et al., 1992).**

Amiel et al. (1991) reported that the intensively treated diabetic patients are more likely to develop EEG abnormalities during hypoglycemia compared with poorly controlled diabetics and normal subjects. Also, **Salem et al. (1994)** stated that, type-1 diabetic patients with severe hypoglycemic attacks showed abnormal EEG findings in those with more than 3 coma attacks. Irreversible intellectual deficits has been related to prolonged,

severe and recurrent hypoglycemia in diabetic children, particularly in young ones **(Soltesz, 1998)**.

In adult IDDM patients, the frequency of severe hypoglycemic episodes has been shown to be inversely correlated with performance in cognitive tests **(Lincoln et al., 1996)**. It should be noted that the relation between repeated hypoglycemic attacks and cognitive dysfunction remains a subject of ongoing debate **(Deary and Frier, 1996)**.

So, the question arises whether or not cognitive impairment in diabetic patients may reflect a central equivalent of peripheral diabetic neuropathy, the so-called central neuropathy or encephalopathy. It should be considered however that, in addition to such an encephalopathy, other factors might influence cognitive function in diabetic patients. For example, the prevalence of psychiatric disorders, in particular, depressive and anxiety disorders is increased in both IDDM and NIDDM **(Peyrot and Rubin, 1997)**.

Diabetes can impair cerebral function and structure. Several pathogenestic mechanisms could be involved. Firstly, factors that are also implicated in the pathogenesis of peripheral diabetic neuropathy could play a role **(Araki et al., 1994)**. As the pathogenesis of peripheral diabetic neuropathy is multi-factorial,

involving metabolic changes neurovascular dysfunction (**Cameron and cotter, 1994**) and changes in trophic support (**Brewster et al., 1994**).

Like in the peripheral nervous system, increased glucose level in the brain leads to enhanced pylol pathway flux (**Kwee et al., 1996**) and accumulation of sorbitol and fructose. However, sorbitol and fructose levels appear to be lower than in peripheral nerves (**Sredy et al., 1991**).

Remarkably, brain myo-inositol content is increased in diabetic rats, contrasting the myo-inositol decrease in peripheral nerves. Enhanced non-enzymatic glycation of neuronal and non-neuronal proteins has also been demonstrated in the brain and spinal cord of diabetic rats (**Pekiner et al., 1993**). Although the level of glycation products in the central nervous system appear to be much lower than in the peripheral nerves (**Ryle et al., 1997**). Also increased concentrations of lipid peroxidation by products, indicative of oxidative damage, have been demonstrated in the cerebral microvasculature and in brain tissue of diabetic rats (**Mooradian, 1995**).

Furthermore, the activity of superoxide dismutase and catalase enzymes involved in the antioxidant defense of the brain, is decreased (**Makar et al., 1995**).

Functional and structural alterations in the cerebral microvasculature of diabetic animals include thickening of capillary basement membrane, capillary density and regional decrease in cerebral blood flow **(Pardridge et al., 1990).**

In diabetic patients, thickening of cerebral capillary basement membranes as well as regional decreases and increases in cerebral blood flow have been reported **(Macleod et al., 1994).**

Treatment of Type-1 Diabetes Mellitus

It includes:

1- Education 2- Insulin therapy

3- Diet 4- Exercise

5- Psychological support

6- Monitoring and measuring diabetes control "Follow up"

7- Pancreas and Islet cell transplantation.

I-Education:

It is fundamental to diabetes management and control. Patients and families need to understand all aspects of diabetes, including acute and long-term complications. They must understand details of insulin action, including duration and timing, injection techniques dietary information, blood glucose monitoring and urinary ketone checks. They must gain skills in integrating the demanding clinical regimen into their schedules, so that they can achieve emotional stability and ongoing psychological growth **(Ingersol et al., 1986).**

Education must be appropriate to the child's age and the family's educational background-shifting responsibilities from parents to child for diabetes self-care skills (eig insulin injection) should be done gradually and when the child shows interest and readiness to do so. Premature shifting of responsibility may cause

deterioration in metabolic control. The life of entire family is affected by having a child with insulin dependant diabetes mellitus. Teaching about and managing diabetes are best handled by a diabetes management team, including a physician, nurse educator, dietitian and psychologist social worker **(Ingersol et al., 1986).**

II- Insulin Therapy:

Insulin Secretion:

a) Endogenous human insulin: It is a cleavage product of proinsulin, is secreted under tight feedback control from the B-cells of the islet of Langerhans.

B) Exogenous Insulin: with identical amino acids to endogenous hormone, is prepared by,

- **Enzymatic conversion of porcine insulin** (alanine is replaced by theorinine at the carboxyl terminal end of the B-chain).
- **Bovine and porcine pancreas** (the allergic effect has been reduced by purification and removal of contaminating peptides).

(Mclellan, 1992).

Routes of Insulin Use:

1- Intravenous (IV): provides the most rapid onset of action and highest peak plasma level, is usually resumed for DKA treatment and preoperative glycemic control.

2- Intramusclar (IM); has no advantage over IV, but is the best alternative if IV route can not.

3- Intraperitoneal: has a role in-patient who is on continuos ambulatory peritoneal dialysis.

4-Subcutaneous (SC): It is the most practical route for healthy diabetic patients. **(Wellington, 1992).**

Insulin Injection Regimens:

The two common insulin regimens in children:

1- Conventional or twice daily mixture of short and intermediate acting insulin.

- **Advantage:**

- Fewer injections
- Good for school children below 10 years who have a rigid routine.

- **Disadvantage:**

- Need to draw up a mixture (although fixed mixtures can be given with the newer pens.
- Must have meals and snacks at set times or risk hypoglycemia.

(Roberston and Edge, 1996)

2-Intensive or multiple-injection regimens, with preprandial doses of short acting and nighttime intermediate acting insulin.

Advantage:

- More flexibility with timing and size of meals.

Disadvantages:

More injections (much scope for forgetting the lunch-time injection). The initial insulin regimen is usually a twice-daily injection of intermediate-acting insulin. This should be two- thirds in the morning and one third in the evening, with a total daily dose of 0.5 unit/ kgm.

During the first two years, once the pancreatic reserve is exhausted, it will be necessary to add a short acting insulin. Prepubertal children generally need around 0.6 to 0.8 units / kg / day, whereas during puberty, this can rise to 1.5 to 2.0 units / kg / day before being reduced again in early adulthood. Most children are now treated with human insulin **(Roberston and Edge, 1996).**

III-Diet:

The diet should contain sufficient protein for growth (2 gm/ kgm / day), mainly carbohydrates (50%) as 10 gm carbohydrate exchanges, some fat (30%); lowering of serum cholesterol and triglycerides is an ideal, but compliance is low if too restrictive.

Total daily calories = 1000 + 100 per year of age. Daily carbohydrates is calculated as 100 gm + 10 gm for each year of life.

Breakfast + morning snack (1/3), lunch + afternoon snack (1/3), evening meal + bedtime snack (1/3). It is essential to maintain a regular intake throughout the day to avoid hypoglycemia **(Habel, 1993).**

Dietary management aims to modify existing eating habits. The emphasis in recent years has moved away from weighting out foodstuffs and counting exchanges, towards, a qualitative judgement of food values. At least half of the energy intake should be from complex carbohydrates.
This usually needs to be in the three meals and three snacks per day the timing of meal leads to the greatest tensions. This is particularly so when snacks need to be eaten during school lessons, or when adolescents can not skip lunch or go out for pizza and chips with their friends. Total prohibition of sweets and chocolate is unrealistic, but these are best eaten at the end of balanced meal. The availability of low-caloric drinks means that beverages do not need to be avoided completely **(Zinman, 1990).**

IV-Exercise:

Children with IDDM should be encouraged to exercise regularly. Since strenuous exercise may result in hypoglycemia due to increased non-insulin dependent uptake of glucose, physical education classes are best scheduled after meals or extra-food should be eaten before exercise. There should be no restrictions on

individual or organized athletic programs because of IDDM **(Stein et al., 1984).**

Physical fitness and regular exercise are important for all patients with IDDM. Insulin requirements may be lower, metabolic control improved and self-esteem and body image better in the physically fit child. During periods of exercise, extra-calories or lower insulin doses may be needed to prevent hypoglycemia. Blood glucose and the response to these therapeutic maneuvers should be done to arrive at an effective regimen for the individual patient. Regular exercise is to be encouraged at any age, because, it then can become part of the child's health care regimen **(Plotnick, 1994).**

V- Psychological Support and Counseling:

The diagnosis of IDDM arouses strong emotional responses in the child and in the family members, including grief, anger, guilt and fear. Although these responses are normal, adjustment to the disease is facilitated by open discussion of these emotions **(Ratzan, 1992).**

VI- Monitoring and Measuring Diabetes Control (Follow up)

Monitoring and recording of blood glucose levels at sufficiently frequent intervals will allow for an adjustment of the insulin dose. For most children and adolescents, testing one to four

times a day provides sufficient information to make insulin adjustments. Many patients do well with a system in which their dose of regular insulin is self-adjusted according to a scale based on the capillary blood glucose level. Insulin adjustment should maintain blood glucose levels as low as possible without unduly increasing the risk of insulin reaction **(Cryer et al., 1989).**

Periodic measurement of glycated hemoglobin or hemoglobin A1c levels allows objective measurement of long-term control in some patients. Non glucose factors as high fetal hemoglobin, hemoglobin S or C, hemolytic anemia may distort the glycated hemoglobin value. In these patients, glycosylated albumin or fructosamine may provide a better objective measure of control. Glycosylated hemoglobin levels vary considerably from one laboratory to another because of differences in methodology **(Allen and Mac Donald, 1986).**

Patients with type-1 diabetes have a higher incidence of thyroiditis which may result in hypothyroidism. Some physicians recommended annual thyroid tests in all patients **(Viberti and Keen, 1995).**

It is hoped that all children or their parents will carry out regular blood glucose monitoring, at least twice a day, urine need only to be tested for ketones when the child is unwell. HbA1c monitoring is a useful tool, and should be carried out at each clinic

visit, generally every three to four months **(Roberston and Edge, 1996).**

VII-Pancreas and Islet Cell Transplantation:

As current forms of insulin therapy are clearly inadequate in terms of long-term morbidity, mortality and short-term risk of severe hypoglycemia, pancreas and islet cell transplantation are being actively studied **(Gill, 1996).** The success of pancreas transplantation, in particular for individuals receiving a kidney transplant has dramatically improved during the past decade **(Sutherland, 1996).**

Newer drug regimens (e.g., replacing azathioprine with mycophenolate mofetil, combined with cyclosporine A and predinsone allowing rapid tapering of glucocorticoid doses to 5 mg predinsone / day within one month). At the same time acute rejection episodes have decreased **(Eisenbarth and Stegall, 1996).**

Most type-1 diabetic patients requiring a renal transplant for diabetic kidney disease should be considered as candidates for a pancreatic transplant. The major indication for pancreatic transplantation is improvement in quality of life with the cure of diabetes. It is likely that except for neuropathy, many of the long-term complications will be little benefited, give extensive disease at the time of renal transplantation **(Eisenbarth and Stegall, 1996).**

The two largest trials for the prevention of type-1 diabetes are the National Institutes of Health DPT- I trial and the primarily European and Canadian ENDIT trial. The DPT-I trial incorporates many of the predictive parameters and is evaluating annual 4 days of insulin infusion and low dose subcutaneous insulin therapy. The ENDTT trial is evaluating oral nicotinamide among first degree relatives selected because of the expression of cytoplasmic islet cell autoantibodies **(Elliot and chase, 1991).**

The rationale for evaluation of nicotinamide relates to the ability of high doses of this vitamin to block the islet toxicity of streptozotocin. It is thought that toxicity involves both the generation of free radicals and the depletion of islet NAD. Studies of NOD mice indicated that high doses of nicotinamide could slow the development of type I diabetes. Finally in a study done by **Elliot and Mandrup-Poulsen. (1996)** treating all school children who expressed cytoplasmic islet cell antibodies with epidemiological comparison to non screened school children, has suggested a 50% delay in progression to diabetes.

The DPT-1 trial is based upon the observation, that subcutaneous and oral insulin (for NOD mice) could prevent (parental insulin) or delay (oral insulin) the development of diabetes **(Zhang et al., 1991).** Subsequent studies demonstrate that insulin is a major target of anti-islet T-lymphocytes and that

therapies such as injection of the immuno-dominant B: 9-23 peptide of insulin is also effective in preventing diabetes **(Daniel and Wegmann, 1996)**. It is though that forms of insulin "vaccination" may function by deviating the T-cells responding to insulin, to T-cells which secrete protective lymphokines **(Calcinaro et al., 1996)**.

Long Term Management of Diabetes Mellitus:

Diabetes programs need to be practical, manageable, and achievable. Therefore, they should be individualized as much as possible within the bounds of reasonable control. For pediatric patients, this often means changing expectations at different developmental seafes. For example, the family of a toddler may be willing to do blood tests four to five times a day **(Glassgow, 1992)**.

Compliance:

In addition to retention of the ability to secrete insulin, the most important factor in achieving good control is the ability of the patient to follow a treatment plan. Even the simplest treatment plan demands considerable patient participation and adaptation. Some patients, particularly during adolescence, find it difficult to make the necessary adjustment. Some patients may not follow the basis, such as constantly taking insulin. Pressure by their family and physician to produce good blood glucose test results. Peer pressure and a desire to confirm may also contribute to deviations from diet

and schedule. It is important to recognize not only when compliance is the problem but also to appreciate that the causes of non compliance lie in our inability to manage diabetes without making considerable demands of patients and their families **(Lesbe and Sperling, 1986).**

This recognition must be balanced with the desire to avoid making over whelming demands on the patient. Nevertheless, the physician can modify the requirements only so much. For example, some consistent pattern of insulin administration is essential. To the extent possible, however, the physician should adjust the diabetes program so that the recommended therapy is only as much as the patient is capable of sustaining. Theoretically, the patient and family should make informed decisions as to the best program for themselves. In practice, however, many patients will look to the physician for guidance **(Lesbe and Sperling, 1986).**

The Diabetic Dyslipidemia

The major lipids of the body; triglycerides, cholesterol, phospholipids and glycolipids play a variety of biological roles. They serve as a primary source of fuel and are important components of cell membranes and many cell structures. They provide stability to the cell membrane and allow for trans-membrane transport **(Cooper et al., 1992)**.

Alterations in the concentrations of major lipids and lipoproteins are well characterized in IDDM. In general, the lipoprotein pattern is anti-atherogenic in IDDM patients who have optimal glycemic control. The concentration and metabolism of plasma lipoproteins in diabetics are influenced first by factors specific to the diabetic state, that is type of diabetes, glycemic control, insulin resistance, transport of free fatty acids, nephropathy (proteinuria) and method of treatment **(Taskinen, 1992)**. Secondly, insulin has multiple sites of action on the metabolism of VLDL-IDL-LDL cascade and HDL. Thus diabetes itself can cause severe perturbations of lipoprotein metabolism **(Taskinen, 1990)**.

In addition to factors that influence serum lipids and lipoproteins in the general population, which operate also in the diabetic population. Therefore, it is expected that the concentration

and composition of an individual lipoprotein can be highly variable and also completely different in people with insulin dependant-diabetes mellitus **(Taskinen, 1988).**

Plasma LDL (LDL-Cholesterol rich) and VLDL (VLDL= Triglycerides rich) levels are elevated and HDL levels are depressed in poorly controlled DM. These abnormalities tend to normalize with improved diabetic control. Elevation of plasma triglycerides level is the most common lipid disorder in both IDDM and NIDDM **(Nikkila, 1981).**

Hypertriglyceridemia in Diabetics:

Elevated plasma triglyceride levels in IDDM has been shown to be a risk factor for CHD among diabetic individuals **(Fontbonne et al., 1989).**

Insulin deficiency in IDDM is associated with decreased clearance of TG-rich particles because lipoprotein lipase activity which depends on the presence of insulin is diminished **(Taskinen, 1992).** Acquired abnormalities of VLDL structure in diabetes may render this lipoprotein less able to interact with lipoprotein lipase, which could impair VLDL catabolism into TG, LDL and IDL **(Banga and Sixma, 1986).**

Hypertriglyceridemia is associated with an increase in the clotting activities of factor VII and factor X and a decrease in the concentration of plasminogen activator inhibitor-1 (PAI-1) thus contributing to the procoagulant state in diabetes **(Bierman, 1992).**

Hypertriglyceridemia in diabetes is also associated with small, dense LDL particles which are more atherogenic than ordinary LDL particles because of their liability to oxidation **(Stern, 1996).**

Hypercholesterolemia in Diabetics:

In diabetic patients, hyper-cholesterolemia can appear as a consequence of elevated VLDL levels, since it carries about 20% of its total lipid content as cholesterol **(Eisenberg et al., 1977).**

Altered LDL metabolism may also contribute to hypercholes-terolemia. The catabolism of LDL may be depressed in poorly controlled diabetics, and in vivo glycosylation of LDL may be involved because this alters the configuration of LDL, so that its reaction with its specific receptor is altered. The reduction of LDL degradation leads to increased levels of plasma LDL and the decrease in its fraction catabolic rate leads to a prolonged half-life of the particles **(Witztum et al., 1982).**

Cowell. (1993), stated that even though LDL-cholesterol levels may or may have not been elevated, there was evidence that a family of small dense LDL particles that existed in diabetics. These particles possibly potentiate atherosclerosis due to its vulnerability to change to oxidized LDL, which was found to be atherogenic even in non-diabetics who had CHD.

Oxidized LDL inhibits endothelium-dependent relaxation and promotes endothelium dependent as well as independent contractions, the consequences are alterations in vasculature, leading to vasospasm and thrombus formation **(Luscher et al., 1993)**.

Diabetic patients with advanced glycosylation end product modification of LDL also showed elevated circulating levels of this type of modified LDL contributing to diabetic dyslipidemia, thereby providing a link between hyperglycemia and atherosclerotic CHD **(Stern, 1996)**.

HDL- Cholesterol in Diabetics:

Plasma HDL-cholesterol levels tend to be decreased during poor metabolic control in IDDM and return to normal after institution of adequate treatment. Alterations of HDL in diabetics are probably based on the presence of insulin deficiency **(Taskinen, 1992)**.

HDL (particularly the subfraction HDL_2) concentration is regulated by two endothelial lipolytic enzymes, lipoprotein lipase and hepatic lipase, both are insulin –sensitive **(Tall, 1990).**

Elevations of HDL-Cholesterol levels in well-treated IDDM patients may reflect improved lipoprotein lipase activity after institution of treatment with insulin **(Nikkila, 1981).**

Salem et al. (1997) reported that diabetic patients with good glycemic control had lower levels of TC, TG, LDL, VLDL, and higher levels of HDL than those with poor glycemic control.

Pathophysiology of Microvascular Disease in Diabetes Mellitus

The Haemodynamic Hypothesis:

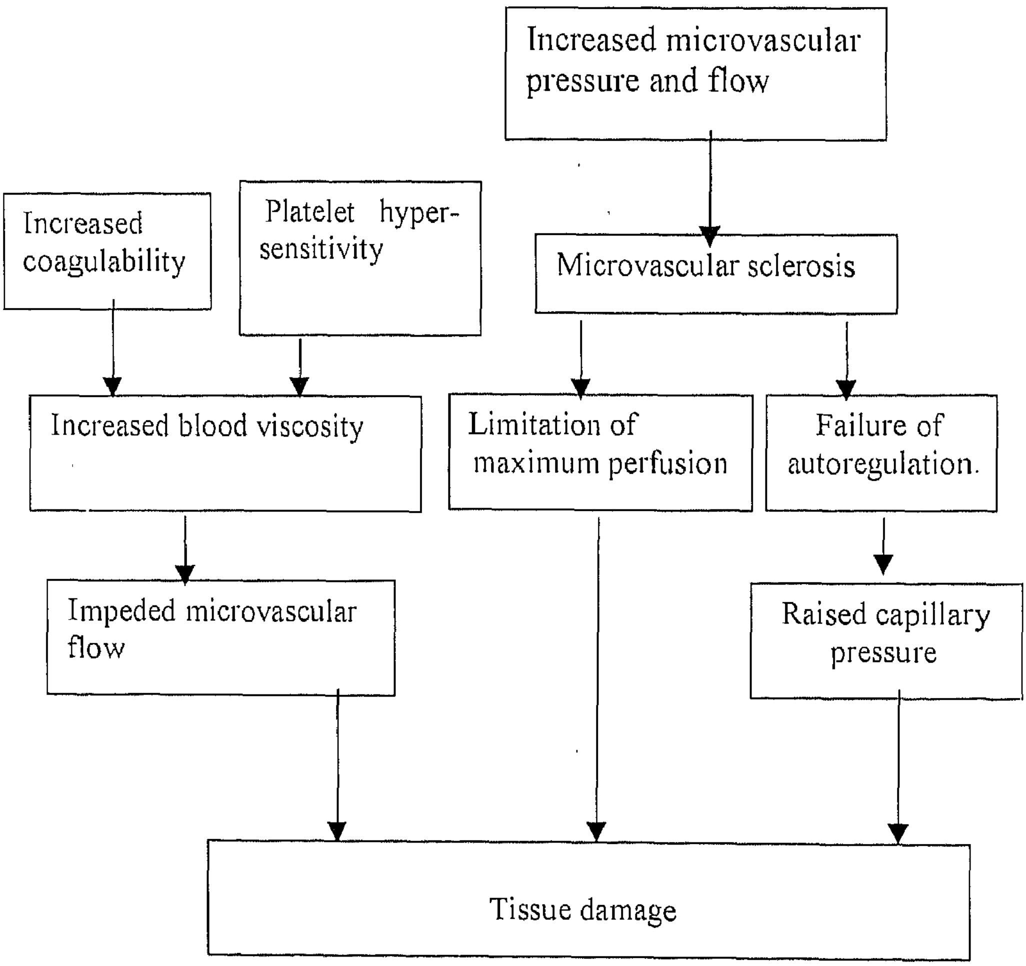
It suggests that haemodynamic changes in the microcirculation could play an important role in the pathogenesis of diabetic micro- angiopathy **(Henriksen, 1986).**

This haemodynamic hypothesis proposes that capillary pressure and flow are increased in the affected tissues, early in the disease. These changes would stimulate the basement membrane thickening and arteriolar sclerosis, which are characteristic of long standing diabetes and which in turn, would limit maximum perfusion and the capacity to autoregulate, several studies have now demonstrated a link between microvascular histological changes and the latter functional abnormalities **(Rayman et al., 1989).**

The elevation of capillary pressure occurs within the first years of diabetic life and is more marked in micro albuminuric patients, who have the greatest risk of developing diabetic nephropathy **(Shore et al., 1992).** Capillary pressure also falls with improvement of glycemic control, for example following three months of intensified diabetic control in patients with IDDM of

relatively short duration (**Sandemamn et al., 1992**), or after acute insulin administration to hyperglycenic insulinopenic individuals (**Sandemamn et al., 1991**).

Figure (2): Shows the haemodynamic hypothesis for the development of diabetic microangiopathy (right) with modifications showing the role of rheological abnormalities (left).



(**Henriksen, 1986**).

Some of the major abnormalities of vascular reaction in diabetic people and animals include exaggerated vasoconstrictor tendency, with enhanced responsiveness to vasoconstrictors such as noradrenaline and impaired endothelium-dependent relaxation for example in response to acetylcholine. However, increased vasoconstriction could for example leads to occlusion of small arterioles in the retina, or to contraction of the efferent arterioles in the glomerulus, which would raise intraglomerular capillary pressure **(Zatz et al., 1986).**

Much interest has focused on the endothelium, because of its dual role in the production of local vasoactive mediators and in controlling platelet adherence to the vessel wall. Abnormalities of nitric oxide (NO) production by the vascular endothelium have been described in patients with IDDM and micro-albuminuria both under resting conditions and in response to acetylcholine **(Elliot et al., 1993).**

There are several potential mechanisms by which diabetes might interfere with endothelial release or action of NO. Acetylcholine receptor abnormalities have been implicated in patients with IDDM **(McNathy et al., 1994)** and NIDDM **(Lawrence et al., 1995).**

Although animal studies suggest that specific receptor abnormalities are not responsible for the observed abnormal acetylcholine response **(Tanz et al., 1989).** It has been suggested that the normally balanced endothelial release of vasodilators and vasoconstrictors may be deranged in diabetes; some evidence from experimental diabetic animals points to increased production or release of prostanoid constrictors, which could attenuate endothelium-dependant vasodilatation **(Shimzu et al., 1993).** Although, this is not a universal finding **(Taylor et al., 1992).**

To be effective, NO must diffuse from the endothelium to the underlying smooth muscle, and various factors have been proposed to interfere with this process in diabetes. Advanced glycation end-products (AGE) **(Bucala et al., 1991)**, glycated hemoglobin **(Rodriguez-Manas et al., 1993)**, free radicals **(Tesfamariam and Cohen 1992)** and oxidized low density lipoproteins **(Bucala et al., 1993)** have all been reported to quench or inactivate NO.

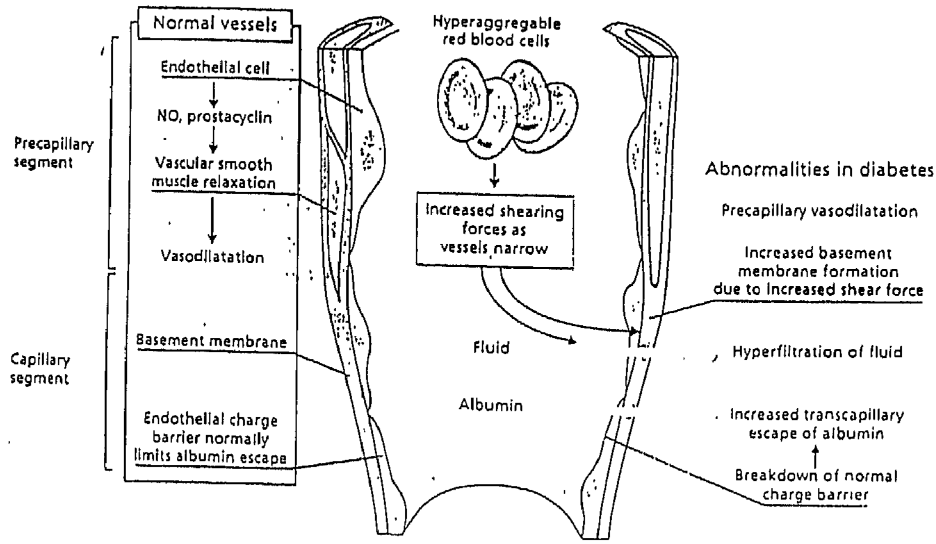
These factors could therefore contribute to the impaired vasodilator responses, whether elicited directly by NO donors or indirectly by agents such as acetylcholine **(Bucala et al., 1993).** Several abnormalities in blood rheology and coagulability have been reported in diabetic patients and by impeding flow in the microcirculation could further impair tissue nutrition. Defects

include increased whole blood and plasma viscosity, increased red cell aggregation, and hypersensitivity of platelets in vitro to various aggregating agents. Increased platelet aggregability has been described in both IDDM and NIDDM patients, and in particular in patients with microalbuminuria **(Winocour, 1992).**

The endothelium is now recognized to play an essential role in regulating platelets adherence to the vascular wall and a reduction in NO production by the endothelium could encourage platelets to stick **(Henderson, 1991).**

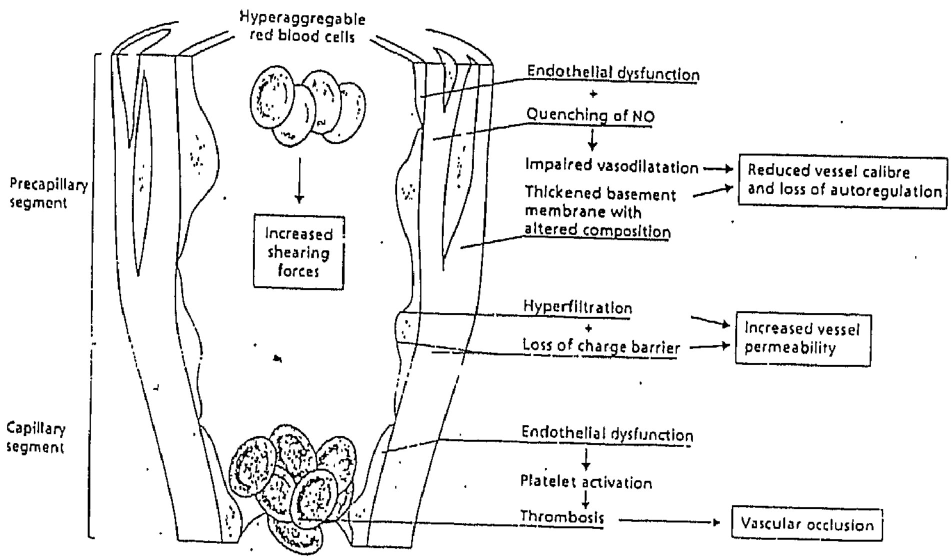
NO synthase has been also identified in human platelets, where it is proposed to have antiaggregation and antiadherence proprieties. It remains to be established whether this function is abnormal in diabetes. Overall, platelets defects could be important in the pathogenesis of microvascular complications **(Radomski et al., 1990).**

Figure (3): Schematic diagram of pathogenic mechanisms that may operate early in diabetic microangiopathy in type-1 diabetes.



(Radomiski et al., 1990)

Figure (4): Schematic diagram of possible pathogenic mechanisms operating in advanced microangiopathy in type-1 diabetes.



(Radomiski et al., 1990)

Initially, precapillary resistance is reduced, increasing flow through the capillary bed. Hyperaggregable red cells are forced to disaggregate as the vessel diameter narrows, so enhancing tangential shear stresses on the microvascular endothelium. This will increase filtration of fluid, as has been shown experimentally and will favor the passage of albumin across the capillary wall. Alterations in endothelial charge further facilitate the loss of albumin. Increased tangential stresses also stimulate the endothelial cell to release vasodilator compounds such as NO and prostacyclin (causing further vasodilatation and discouraging adherence of platelets), and to synthesize basement membrane components **(Forstermann et al., 1994).**

The capillary basement membrane thickens but becomes increasingly permeable, because of the diabetes-induced chemical modifications, which result in net loss of the anionic charge that determines electrostatic integrity. In established disease, the capillary wall has thickened (sclerosis) and this effectively limits maximum vasodilatation. The endothelium may be denuded to expose the subintima, as occurs in the retinal circulation. Abnormal endothelial function in the peripheral circulation allows activation and aggregation of platelets **(Radomski et al., 1990).**

Accumulation of advanced glycation end (AGE) products, free radicals and oxidized lipoprotein may quench locally produced

NO, further impairing vasodilatation and also causing platelets to aggregate and adhere to vessel wall so auto-regulation of pressure and flow becomes progressively impaired. The local fine-tuning of precapillany resistance, which normally regulates vasomotion and ensures uniform distribution of blood flow in the tissue, breaks down, causing patchy perfusion. Increased shunting of blood through arterio-venous anastomoses results in microvascular steal which by passes the capillary bed and compromises tissue nutrition **(Junger et al., 1989).**

Cerebrovascular Disease and Cerebral Blood Flow in Diabetes Mellitus

Diabetes is associated with an increased prevalence of hypertension and cerebrovascular disease **(Monkovsky et al., 1997).** Diabetic vascular disease is characterized by being more severe, diffuse and accelerated than that of non-diabetics **(Santilli et al., 1992).**

Cerebrovascular disease increases the risk of stroke and may lead to haemodynamic changes **(Biller and love, 1993).** These haemodynamic alterations are reflected in the form of regional alterations in cerebral blood flow. In addition, cerebral vasoreactivity is impaired in diabetic patients **(Albert et al., 1993).** Cerebral vasoreactivity and accompanying changes in blood flow, are important compensatory mechanisms during conditions such as hypoglycemia, hypotension, hypoxia and hypercapnia. Loss of these compensatory mechanisms may have detrimental effects on the brain (**Kastrup et al., 1996).**

Diabetic vascular disease is characterized pathologically by endothelial cell hyperplasia and basement membrane thickening **(Sank et al., 1994).** Thickening of basement membranes of capillaries and atherosclerosis occur as a chronic complication

affecting both the microvasculature and macrovasculature **(Lynch and Exton, 1992).**

The thickening of the basement membranes caused by cross-linking of the collagen and carbohydrates, results mainly from hyperglycemia. In the retina and possibly in the cerebral vessels, there is an increase in the capillary diameter, a decrease in the number of pericytes, an increase in the vascular permeability and an increase in micro-aneurysms. Due to these structural changes, the vessels appear to loose the ability to regulate blood flow **(King et al., 1994).**

These vascular abnormalities and vascular structural damage develop early in human and experimental animals **(Dolgov et al., 1982).** There is experimental evidence to suggest that diabetic hyperglycemia triggers a cascade of biochemical abnormalities which lead to early structural damage and vascular dysfunction, ultimately microvascular sclerosis and failure of capillary function will occur **(Knudsen et al., 1991).** Endothelial cells are structurally and functionally altered by diabetes **(Vallence et al., 1992).** An increase in the concentration of soluble endothelial cells markers provides evidence of endothelial cell dysfunction in diabetics, these endothelial markers include: endothelin, elevated levels of Von-Willebrand factor, soluble thrombomodulin, angiotensin-converting

enzyme activity and the accumulation of advanced glycosylation end products (AGE) (**Sank et al., 1994**).

Diabetes induced changes in endothelial cell function may precipitate clinical episodes of vasospasm (**Tesfamariam, 1994**). Contributing factors to the vasospasm are oxygen free radicals and thromboxan-A_2. There is considerable evidence suggesting that the generation of oxygen free radicals is increased in diabetics. Oxygen free radicals destroy nitric oxide and have proven to be potent vasoconstrictors. Furthermore, several studies have shown that diabetes promotes the generation of endothelium derived vasoconstrictor prostagnoids such as thromboxan-A_2 which is a potent smooth muscle constrictor (**Hunt et al., 1990**).

Dandona et al. (1978) in their study on 59 diabetics whom their ages ranged between 14 – 74 years with a mean age of 46 years compared to 28 age and sex matched healthy controls. They measured cerebral blood flow using Xe^{133} inhalation technique using CO_2 as a vasodilatory stimulus. They reported a significant reduction in basal cerebral blood flow as age increases and a significant reduction of cerebral vasoreactivity in 26 patients after using CO_2 challenge and this impaired cerebrovascular reactivity involved those with long term disease and some of the newly diagnosed cases.

Also, **Crougwhell et al. (1990)** in their study on eleven IDDM patients with a mean age of 60 ± 9.1 years compared to age and sex matched 12 non-diabetic patients, all are facing CPB for coronary atherosclerosis. They measured cerebral blood flow using Xe^{133} clearance method. Cerebral blood flow was measured in both hypothermic (at ≤ 28°C) and normothermic (at ≥ 36.5°C) states. They detected impaired cerebral autoregulation at hypothermic state in diabetics facing CPB compared to the non-diabetic patients. They stated that diabetic patients on CPB compensate for unbalances in adequate oxygen delivery by increasing the amount of oxygen extracted from cerebral blood. These patients may be at increased risk for cerebral ischemia during low flow or low pressure as seen with CPB **(Schell et al., 1993).**

Also, **Rodriguez et al. (1993)** in their study on 20 IDDM patients whom their ages ranged between 16-55 years with a mean age of 25.64 ± 8.35 years and a disease duration ranged between 1-36 years with a mean duration of 12.29 ± 9.76 years compared to 15 age and sex matched healthy volunteers. They had measured CBF using Xe^{133} inhalation method and cerebrovascular reactivity evaluated as pre and post ACZ rCBF difference. They found a significant positive correlation between basal cerebral blood flow and diabetes duration and found no significant correlation between cerebravascular reactivity and glycemic control and also failed to

detect a linear correlation between cerebral vasoreactivity and diabetes duration. Although they found no linear correlation between cerebrovascular reactivity and disease duration, yet among 5 patients with a disease duration more than 20 years, 3 patients had poor response to ACZ (poor reactivity).

Latter on, **Fulsedi et al. (1997)** in their evaluation of cerebral blood flow and vasoreactivity in 72 type-1 diabetics (36 women and 36 men: mean age 36.4 ±8.9 years; mean diabetes duration, 15.5 ± 9.7 years) categorized into two subgroups; the first one with a disease duration less than 10 years, the second one with a disease duration more than 10 years compared to 40 age and sex matched non diabetic healthy controls (20 men and 20 women with mean age, 39.3 ± 11.4 years). They found no significant change in cerebrovascular reactivity in those with a disease duration less than 10 years compared to controls, but the cerebrovascular reactivity was significantly low in diabetics with a disease duration more than 10 years compared to either group of short duration or controls and cerebrovascular reactivity is inversely correlating with disease duration.

Meanwhile they detected no significant change in basal cerebral blood flow among the 2 diabetic subgroups compared to controls.

Relation of Haemodynamic Changes in Type-1 Diabetes Mellitus to Microangiopathy

Early haemodynamic disturbances have been demonstrated in type-1 diabetic patients, including increased basal blood flow in various organs including the kidney, retina and limbs, together with relatively impaired responses to various hyperemic stimuli in the skin. These changes occur early in IDDM before evidence of structural microvascular damage appears. The increased capillary pressure and flow in the relevant tissue early in the disease, acts as a stimulus to the basement membrane thickening and arteriolar sclerosis which are characteristics of long-standing diabetes and which in turn limit maximum perfusion and the capacity to autoregulate (**Rayman et al., 1989**).

Factors that may contribute to worsening of haemodynamic disturbances:

Clinically significant microangiopathic complications are rarely seen before puberty, but the rate is faster in post-pubertal years (**Shone et al., 1989**). The likelihood of developing microangiopathy rises with increasing disease duration (**Rayman et al., 1989**).

One possible explanation for the lack of a direct relationship between glycemic control and the development of microangiopathy is that there may exist subsets of patients who are less vulnerable to the effect of sustained hyperglycemia **(Tooke et al., 1987 and Kobbah et al., 1988).**

There is some evidence for this, in that those patients who have survived IDDM for over 40 years without developing nephropathy or significant retinopathy display normal non-neurogenic microvascular responses, although neurally dependant mechanisms may be impaired **(Tooke et al., 1987).** Maximum cutaneous perfusion capacity is also relatively preserved in patients with uncomplicated disease of long duration **(Walmsley et al., 1989).**

Also, changes in microvascular reactivity could also explain the acute deterioration in microvascular disease especially retinopathy which is sometimes observed when glycemic control is suddenly and markedly improved, the so called glycemic re-entery phenomenon. Autoregulation that means (the capacity of the micro-circulation to maintain constant flow in the face of a changing pressure head) fails in patients with diabetes of moderate duration and this failure could exacerbate the haemodynamic changes caused when blood glucose levels are lowered **(Grunwald et al., 1983).**

Such changes include a reduction in plasma volume, increased sympatho-adrenal activity and a rise in blood viscosity; hypoglycemia-an inevitable consequence of tightened glycemic control tends to encourage coagulation and may also raise blood pressure transiently. If auto-regulation breaks down, increased systemic pressure will be transmitted to the microvascular bed, raising capillary pressure and causing tissue damage. The retina would be especially vulnerable, as its high metabolic demands are normally closely matched to its nutrient supply; a sudden reduction in glucose availability may therefore seriously compromise retinal metabolism until adaptive changes have occurred **(Frier and Hilsted, 1985).**

A transient but sometimes marked advancement of nephropathy and retinopathy may occur during pregnancy; the physiological changes in microvascular haemodynamics which accompany pregnancy may offer a ready explanation **(Phlips et al., 1986).**

Haemorheologic and Coagulability Changes in Diabetic Patients

Red Cell Deformability:

Red cell deformability is the ability of the red cell to change shape in response to external stresses. Thus, it may be redefined as those physicochemical characteristics with permit the erythrocyte, whose greatest diameter normally exceeds 7 μm, to pass through normal capillaries which range from 3 to 12 μm in diameter **(Buchan, 1980)**. The deformability of erythrocytes is important in three situations; Firstly, it is an important determinant of erythrocyte life span in vivo **(Weiss, 1972)**. Secondly, it has a significant influence on blood flow in the peripheral circulation **(Jay et al., 1972)**. Thirdly, it is a determinant of whole blood viscosity, particularly at high rates of shear, and so it affects peripheral resistance and hence cardiac work **(Chein 1976)**.

Red cell deformability has been discussed for the first time at the end of the seventeenth century by Van Leewvenhoek **(Marcel, 1979)**. It is determined by three major factors:

(1) the geometry of the cell,

(2) the viscosity of the intracellular hemoglobin; and

(3) the physical properties of the red cell membrane **(Hanns and Koutsouris, 1989)**.

Another evidence suggests that this definition should be extended to encompass not only the morphological changes in the red cells that occur under stress, but also the rheological changes, their flow behavior under stress. The importance of this property in vivo is twofold. Firstly, it allows individual red cells, whose mean resting diameter is 7.5 μm, to traverse nutritive capillaries with diameters between 3 and 5 μm. Secondly, red cell deformability allows a reduction in the viscosity of bulk blood flowing in large vessels, since shear forces result in red cell deformation, alignment of the cells with its longitudinal axes parallel to the fluid stream line, and participation in flow **(Lowe, 1981).** The change in the shape of the normal erythrocytes during their passage through minute vessels had been demonstrated by direct microscopic observation **(Chien, 1976).**

The importance of red cell deformability in medicine is also twofold. Firstly, in almost all types of hemolytic anemais, decreased red cell deformability may allow the removal of red cells from the circulation by trapping in splenic sinuses. Secondly, reduced red cell deformability in patients with diabetes mellitus and peripheral vascular disease might impair red cell deformation in nutritive capillaries and hence contribute to tissue ischemia. Conversely, pharmacological improvement of deformability might be of therapeutic value in such patients **(Lowe, 1981).**

Abdul Ghani et al. (1990-a) in their study on diabetic children, free of any vascular complications, they found a significant decrease in RBCs filterability (Deformability) compared to healthy controls but **Sandhagen et al. (1997)** reported no significant change in RBCs deformability and fibrinogen level in short term type-1 diabetics with a disease duration less than 5 years while other investigators proved the association between impaired RBCs deformability and the long term type-1 diabetics especially those with poor glycemic control **(Juhan et al., 1982; Bareford et al., 1986 and Linderkamp et al., 1999).**

Fibrinogen :

Fibrinogen is a glycoprotein of molecular weight approximately 3400 daltons, present in the plasma at a concentration in the range of 150 to 350 mg/dL **(Hoeprich and Doolittle, 1983).** It is synthesized in the liver, with a steady state, synthetic rate of 1.7 to 5gm /day and by megakaryocytes **(Reeve and Frank, 1974).**

The synthesis of fibrinogen is controlled by the gene, which codes for the B-chain synthesis. Due to the existence of a genetic polymorphism for this gene, the plasma level of fibrinogen varies according to the individuals. The plasma half-life of fibrinogen is about 3-5 days **(Collen et al., 1972).**

About 75% of the body's fibrinogen is found in the plasma but it is also distributed in the interstitial fluid and lymph. An additional fibrinogen pool exists in platelets but it is metabolically, functionally and structurally different from plasma fibrinogen **(James et al., 1977)**. As an acute phase reactant, fibrinogen increases in concentration in response to a variety of physiologic stresses such as trauma, pregnancy, tissue inflammation and the injection of biologic products such as growth hormone, thrombin toxin and prostaglandins **(Aronsen et al., 1972).**

An association between elevated fibrinogen level and atherosclerotic coronary artery disease has led to efforts at defining the genetic, cultural and other variables that contribute to the blood population scatter in fibrinogen levels **(Meade et al., 1986).**

Procogulant State in Diabetes:

Patients with diabetes mellitus have a reduced life expectancy in spite of the fact that improved glucose control has decreased metabolic complications sharply. Now, mortality is determined predominantly by vascular events, which frequently have a complicated follow up. Diabetes is a vascular risk factor by itself **(Tschoepe et al., 1993).**

It is a common finding that diabetes is associated with a hyper-coagulable state **(Banga and Sixma, 1986)**, as diabetic

patients exhibit hyperactive platelets at injured endothelial interfaces acting together with an increased availability of thrombotic precursors, reduced coagulation inhibitors and diminished fibrinolysis **(Stout, 1987).**

Ganda. (1985) documented that fibrinogen concentr-ations are frequently elevated in diabetes, regardless of diabetes duration, but particularly in those with type-II diabetes and pre-existing vascular complications. Also **Zimmermann et al. (1996)** reported a significant increase in plasma fibrinogen concentration in type-1 diabetic patients with micro-albuminuria and those with overt nephropathy with a disease duration more than 15 years compared to normo-albuminuric patients.

In another study **Fulsedi et al. (1997)** reported a significant increase in fibrinogen level in type-1 diabetic patients with a disease duration more than 10 years compared to either controls or those of short disease duration (Duration less than 10 years) and fibrinogen level is inversely correlating with the vasodilatory ability of cerebral vessels.

On the other hand, **Coller et al. (1978)** found no appreciable increase in fibrinogen levels in those without retinopathy whereas those with retinopathy had striking elevations. As fibrinogen is one of the important plasma proteins that contribute to the blood

viscosity, increased blood viscosity is associated with an increased risk of atherosclerosis **(Velican and Velican, 1980).**

Zimmermann et al. (1996) recorded a significant increase in plasma viscosity in type-1 diabetic patients with overt nephropathy and documented that plasma viscosity and erythrocyte aggregation are mainly affected by plasma protein composition particularly fibrinogen that considerably affects blood rheology but **Sandhagen** et al. (1997) found no significant change in plasma viscosity, erythrocyte aggregation in short term type-1 diabetics with a disease duration less than 5 years compared to healthy controls.

Also, it has been reported that fibrinogen excess might contribute not only to the vessel wall pathology but it may even exacerbate the diabetic vasculopathy, rather than simply being a marker for pre-existing disease **(Velican and Velican, 1980).**

However, **Jones et al. (1984)** found that shortened fibrinogen survival was reversible by correction of hyperglycemia. Therefore, it is possible that acute fluctuations in glycemia play an important role in thrombin activation in the presence of elevated fibrinogen concentrations.

Garcia et al. (1974) reported that traditional risk factors (hyperlipidemia, hypertension, smoking, age and obesity) do not account fully for the increased prevalence and severity of vascular disease in diabetes.

Ganda and Arkin. (1992) documented that fibrin deposition has a role in the development of atherosclerotic lesions, such observations provide support for the theory of thrombogenesis in evolution of atherosclerosis. Increased clotting potential or fibrinogen levels which is prevalent in diabetes may form a more rigid fibrin gel structure, which might be more thrombogenic **(Jorneskoy et al., 1996).**

The structure of a clot is made by fibrin, which is delivered from fibrinogen when activated by thrombin. Alterations in the fibrin gel structure have been described in diabetic patients during poor metabolic control **(Nair et al., 1991).**

The tighter and more rigid fibrin gel structure decreases the availability of fibrinolytic enzymes to reach their binding sites leading to impaired fibrinolysis **(Williams et al., 1995).** The altered fibrin gel structure may be due to increased glycosylation of fibrinogen and fibrin and may be of importance for the development of angiopathy in diabetic patients **(Fatah et al., 1996).**

Also, **Geiger and Binder.(1988)** reported that glycation of plasminogen may result in its impaired activation by plasminogen activators, and glycation of platelet membrane protein complex II-b, III-a which is a platelet receptor for fibrinogen may account for the increased platelet aggregation in diabetes. Impaired fibrinolytic activity revealed that tissue plasminogen activator in diabetics is present in normal or increased amounts in the plasma, but is biologically inactive because it is bound in a complex with its inhibitor. This binding occurred in both IDDM and non-insulin dependent subjects **(Kwaan, 1992).**

Salem et al. (1996) found a significant decrease in tissue plasminogen activator activity levels in patients with type-1 diabetes in comparison to control subjects which could be explained by poor glycemic control as a predisposing factor for microangiopathy and vasculopathy resulting in a decrease in endothelial secretion of tissue plasminogen activating factor activity.

Also, **Salem et al. (1996)** reported that in type-1 diabetes, there is a decreased level of tissue plasminogen activating factor activity with hypofibrinolytic state resulting in increased risk of thrombotic complications. This risk is increased by bad glycemic control especially in micro-albuminuric patients who have hypertension.

Ganda. (1985) reported that of considerable interest is the relationship of fibrinogen with vascular complications, not surprisingly, the patients with complications were older, had longer duration of diabetes, poorer control, and higher cholesterol levels.

Kwaan. (1992) documented that changes in the hemostatic components and in the plasminogen-plasmin system may not only cause the increased thrombo-embolic risk in diabetics, but also, may play an important role in the pathogenesis of vascular complications including atherosclerosis and microangiopathy.

Assessment of Cerebrovascular Reactivity and Autoregulation

Cerebrovascular reactivity refers to the responses of the cerebral arterial tree and the cerebral blood flow (CBF) to specific vasoactive substances as Acetazolamide (Diamox). In individuals not receiving vasoactive pharmacologic agents, the major physiologic modulators of cerebrovascular resistance are CO_2 and O_2 **(Babikian and Schwarze, 1996).**

Assessment of normal vasoreactivity in normal subject can be done by hyperventilation where the flow velocity will decrease within 15 seconds from the onset of hyperventilation **(Malatino et al., 1992).** It can drop by 35.3% from base values **(Ringelstein et al., 1988).**

They increase by as much as 52.5% during hypercapnia. When 1 gm of Acetazolamide (Diamox) administered IV, the effect will be observed within less than 3 minutes, when the flow velocities are measured in the middle cerebral artery (MCA) after injection of Acetazolamide **(Piepgras et al., 1990).**

This increase lasts more than 30 minutes and gradually decreases afterwards. This vasoreactivity can be evaluated by either

CBF techniques **(Bishop et al., 1986)**, or transcranial doppler sonography **(Widder et al., 1986 and Ringelstein et al., 1988).**

The perfusion pressure of the brain can not be measured directly in humans. Parameters indirectly reflecting cerebral perfusion pressure are the regional cerebral blood flow (rCBF), the regional cerebral blood volume (rCBV) ratio, evaluated by either positron emission tomography (PET) or single photon emission computerized tomography (SPECT) **(Gibbs et al., 1984 and Bull et al., 1988)** and the vasoreactivity which can be tested by either TCD or PET or SPECT techniques. Testing of cerebral perfusion pressure by PET or SPECT or TCD has an important application, since maintaince of cerebral perfusion pressure is a prerequisite for the prevention of cerebral ischemia.

Physiological fluctuations in systemic perfusion pressure and how far cerebral perfusion pressure changes can be compensated by cerebro- vascular autoregulation. PET, SPECT and rCBF techniques deliver two flow volume values with a relatively good spatial resolution of flow data but have the disadvantage of a very poor temporal resolution. In contrast, TCD deliver flow velocity data, giving a value for the whole vascular territory under study and has the unique advantage of an excellent time resolution in the millisecond range, this makes TCD the only available blood

flow measurement technique to answer certain scientific questions **(Aaslid, 1987).**

Early investigations of cerebrovascular reactivity used CO_2 as a physiologic stimulus, but later Acetazolamide was preferred. An advantage of CO_2 is its ability to test the reactivity of the cerebral vasomotor reactivity in both directions, with vasodilatation under hypocapnia by hyperventilation. At $PaCO_2$ levels in the range between 38mm Hg to 42 mm Hg, the CBF increases by about 4% for each mm Hg increase of $PaCO_2$. The flow drops of the same range corresponding to similar decreases of the $PaCO_2$ in hypocapnia **(Norrving et al., 1982 and Vorstrup et al., 1986).**

According to **Lassen and Astrup (1990)**, the effect of CO_2 is mediated by the pH of the arteriolar smooth muscle cells which depends on the blood CO_2 and intracellular HCO_3 contents, however in clinical practice CO_2 has certain disadvantages, a major problem arises from the fact that, the patients with chronic lung disease can not reliably be tested. Patients with severe illness in the acute stage or those with coronary heart disease and congestive heart failure would not be able to stand the considerable physical work of hyperventilation.

In contrast, Acetazolamide testing is influenced by the patient cooperation. Comparative studies on the effect of CO_2 and Acetazolamide on cerebral vasomotor reactivity (VMR) revealed

rather similar results with the two techniques with Acetazolamide being slightly superior **(Ringelstein et al., 1988).**

Cezernick et al. (1994) studied the effect of Acetazolamide on early ischemic cerebral oedema in gerbils and suggested that Acetazolamide seems to be useful for cerebrovascular response studies in the early stages of brain lesion.

Muller et al. (1995) compared breath-holding maneuver (as a carbon dioxide-dependent vasodilating stimulus) with the Acetazolamide challenge by means of transcranial doppler sonography. Their conclusion was that the assessment of vasomotor reactivity (VMR) by TCD correlates with cerebral blood flow changes even when different vasodilatory stimuli are used. Both stimulation techniques similarly indicated significantly reduced VMR with increasing degree of internal carotid artery lesions, but the Acetazolamide challenge differentiated more accurately between the various groups of internal carotid artery findings.

Leinsinger et al. (1994) investigated the normal values of cerebral vascular reserve capacity after stimulation with Acetazolamide measured by Xe^{133} SPECT to determine whether a standardized stimulation challenge with Acetazolamide will be helpful for assessing the vasodilator capacity in patients with obstructive cerebrovascular diseases. They concluded that the standardized challenge with Acetazolamide seems to be a reliable

method to determine cerebrovascular reserve capacity quantitatively.

Although, the CO_2 or Acetazolamide induced vasomotor response is generally used as an indirect parameter of cerebral perfusion pressure, yet this does not necessarily parallel autoregulation in every instance. In the so called post–ischemic hypoperfusion for instance, a dissociation between pressure dependant autoregulation and CO_2 or Acetazolamide induced reactivity may occur **(Schmidt-Kastner et al., 1987)**.

Responses of the cerebral vasculature to hypotensive stress occur so rapidly that the classical rCBF measurement techniques are not able to measure these changes due to their poor temporal resolution. TCD sonography, by contrast, has an excellent resolution, thus allowing on line measurement of even very rapid responses in CBF velocity induced by short lasting modulations of the systemic arterial pressure **(Ringelstein and Otis, 1992)**.

Cerebrovascular Circulation
Anatomy and Collateral Pathways

The vascular system of the human brain differs significantly both anatomically and physiologically from other organs in the body. Although, it accounts for only 2% of the body weight, the brain receives 15% of the cardiac output and consumes 20% of the body oxygen supply in the basal state: Cerebral arteries are little influenced by sympathetic nerves, unlike other arteries, but they are markedly affected by Chemical changes in the blood **(Diethrich, 1992).**

The brain is supplied directly by four vessels; the two internal carotid arteries and the vertebral arteries. The blood supply for the central nervous system derives from the three great vessels arising from aortic arch in the superior mediastinum; the innominate artery, the left common carotid artery and the left subclavian artery. The innominate artery travels up wards, slightly posteriorly from the arch of the aorta to the right of the neck for its 4 to 5 cm length, dividing into the right common carotid artery and the right subclavain artery at the upper border of the right sternoclavicular junction **(Williams, 1995).**

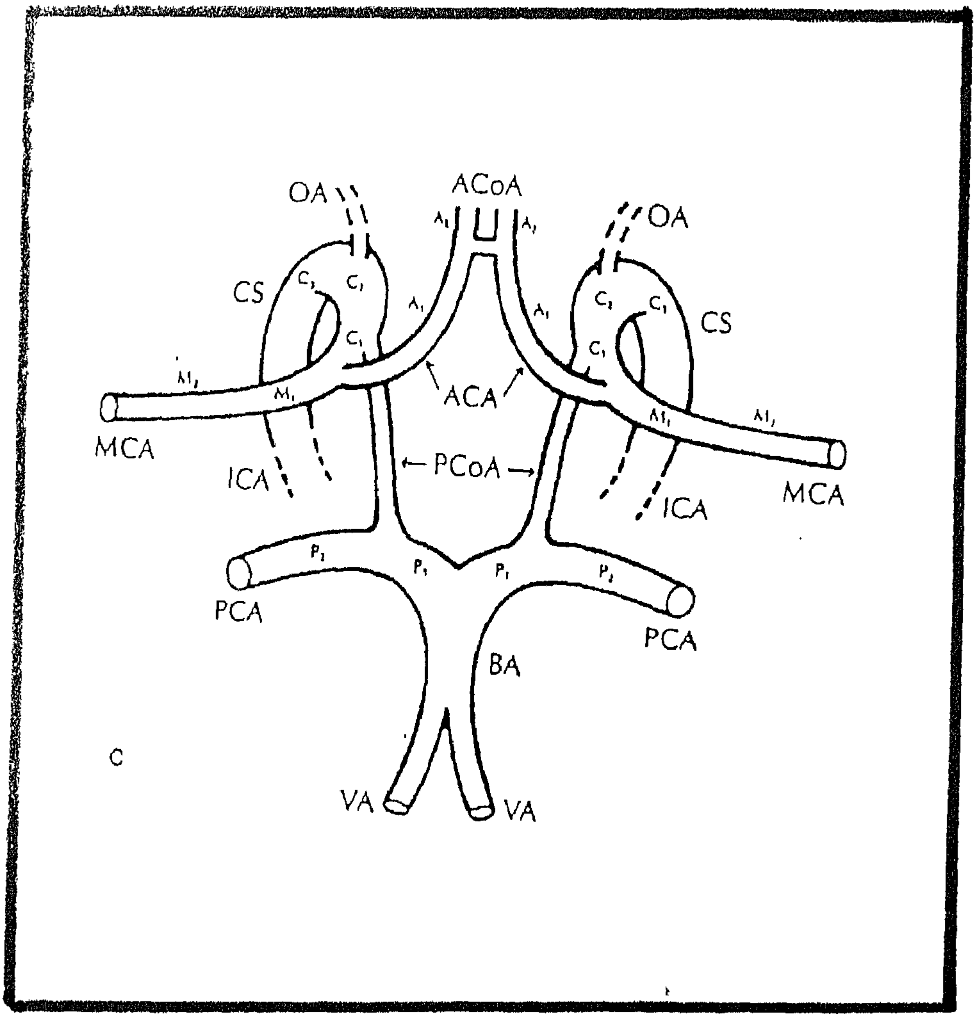
Neither common carotid arteries has collateral branches, but each divides into the internal and external arteries at the level of the upper border of the thyroid cartilage. The internal carotids supply most of the anterior circulation to the cerebrum. There are no branches of the internal carotid arteries in the neck. As, they proceed intracranially, the internal carotid arteries give rise to the carticotympanic branches in the petrous bone, the meningeo-hypohyseal branches in the cavernous sinus region, and the ophthalmic arteries immediately distal to the cavernous sinus. Beyond the clinoid process, within the dura matter, the internal carotid arteries give rise to the posterior communicating arteries, which join with the posterior cerebral arteries **(Williams, 1995).**

The internal carotid arteries divide into the middle and anterior cerebral arteries and give rise posteriorly to the anterior choroidal arteries. The external carotid arteries normally supply no blood to the brain. However, several of their branches can become important collateral pathways if occlusion occurs in the internal carotid arteries or vertebral arteries. The branches of the external carotid artery are the ascending pharyngeal, the superior thyroid, the lingual, the external maxillary, the occipital, the fascial, the posterior auricular, the internal maxillary, the transverse fascial and the superficial temporal arteries. The external carotid branches most vital to collateral circulation are those in communication with the

ophthalmic artery and those that interconnect between the muscular branches of the occipital and vertebral arteries **(Williams, 1995).**

The posterior circulation into the brain is supplied in large part by the vertebral arteries arising from the subclavian arteries. The vertebral arteries lie within the foramen transversalis of the upper cervical vertebrae and wind anteriorly into the subarachinoid space at the side of the medulla oblongata at the level of atlanto-occipital interspace. They reach the ponto-medullary level and then join to form the basilar artery. Four branches arise from the basilar artery as it courses upwards before dividing into the posterior cerebral arteries. Branches of the basilar artery supply the entire pons and the superior and anterior aspects of the cerebellum. Branches of the vertebral arteries supply the medulla and inferior surface of the cerebellum **(Williams, 1995).**

The cerebral branches of the internal carotids and vertebral arteries are joined at the base of the brain by an arterial circle known as circle of Willis. This anastomosis is the most important element is intracranial collateral circulation and is also a common site of aneurysmal formation. It is a hexagonal arrangement of arteries composed of the anterior, middle and posterior cerebral arteries, which are joined by the anterior and posterior communicating arteries. So, in cases of arterial occlusion in the carotid or vertebro-basilar vessels, this circle opens to function as a vital collateral pathway **(Williams, 1995).**



(Williams, 1995)

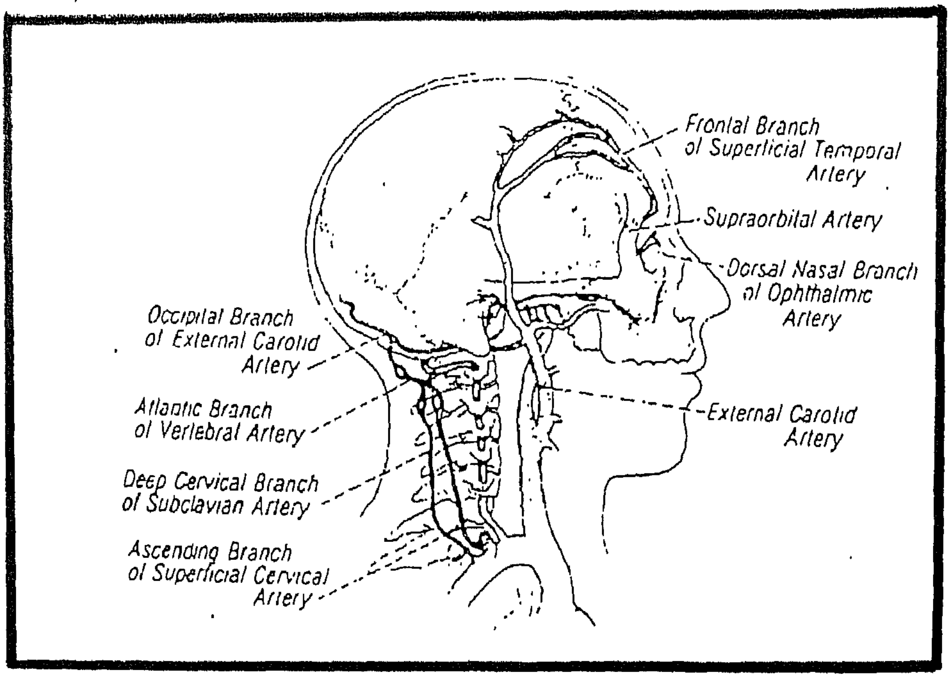
Figure (5): Basal cerebral arteries of the circle of Willis (OA, ophthalmic artery; CS carotid siphon (Cl C3); ICA, internal carotid artery; ACA, anterior cerebral artery (Al A2); ACOA, anterior communicating artery; MCA, middle cerebral artery (M1, M2); PCA posterior cerebral artery (p1, P2); PCOA, posterior communicating artery ; BA, basilar artery; VA, vertebral artery).

Collateral Pathway of The Brain Circulation

The vital role of collateral circulation in vascular occlusion has been appreciated as it is involved in cerebrovascular occlusive disease as an important diagnostic item. There are two types of arterial branches supplying the brain. The more important type in terms of neuronal function and nutrient supply for the central nervous system is the penetrating arteries. However, its diffuse, circumferential or superficial arteries that spread over the entire surface of the hemispheres, brain stem and spinal cord through which collateral circulation takes place **(Dieth rich, 1992).**

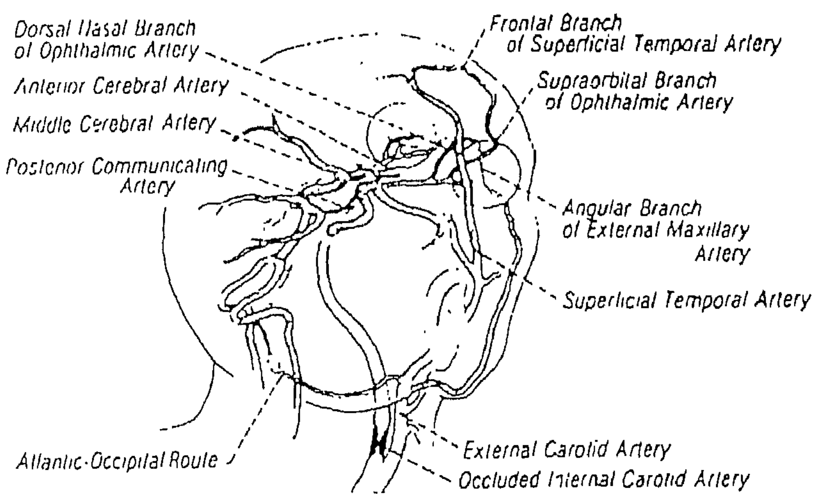
The routes for intracranial collateral circulation can be divided into three catigories; large interarterial connections, intracranial-extracranial amastomosis, and small interarterial communications. The major pathway is the circle of Willis, providing communications between the two carotid arteries or between the basilar artery and the right or left carotid artery. Second to the circle of Willis in importance is the complex of intracranial-extracranial (Prewillisian anastomosis). Perhaps, the best-known prewillisian anastomosis is that between external and internal carotid arteries, through the orbital and ophthalmic arteries. Other external to internal carotid collaterals include the

meningeohypophyseal and corticotympanic branches. Other important prewillisian anastomosis that may be encountered clinically include the following; the occipital branch of external carotid artery in communication with the Atlantic branch of vertebral artery, the deep cervical and ascending cervical branches of subclavian arteries connecting with the branches of the lower vertebral, the Atlantic branch of upper vertebral artery and the occipital branch of the internal carotid artery and the external carotid arteries communicating across the midline (**Diethrich, 1992**).



(Diethrich, 1992)

Figure(6): Extracranial cerebrovascular anatomy. The anastomotic connections between the external and internal carotid arteries and among the occipital, cervical and vertebral arteries.



(Diethrich, 1992)

Figure (7): Major external carotid and vertebral collatral pathways assoated with internal carotid occlusion.

Of lesser importance, are the leptomeningeal collaterals forming the meningeal border-zone network. These connect the terminal cortical branches of the main cerebral arteries across the border zones along each vascular territory. Although these are not major collateral pathways, they may be sufficiently to overcome the arterial occlusion. Since, the leptomeningeal anastomosis can give excellent collateral blood flow around the thrombosed cortical vessel and induce rapid clearing of the neurologic deficit **(Diethrich, 1992).**

The opening of the collateral pathways is dependent largely on the age of the individual and the time of sequence of occlusion. In older individuals, collateral pathways are more likely to be hypoplastic or involved in the atherosclerotic process. Even collateral vessels of sufficient luminal size are often not able to adapt rapidly with the sudden occlusion (eig emboli). Also, when, there are multiple atherosclerotic lesions present, the adequacy of the collateral channels may be greatly lessened. Lastly, affecting the adequacy of a collateral bed are the availability of multiple rather than single collateral sources and the pathologic conditions of the vessels, reducing their capacity for dilatation **(Diethrich, 1992).**

Transcranial Doppler Sonography

Transcranial Doppler Sonography, relaying on innovations in both technology and technique, has proven to be clinically useful tool in a variety of established and developing applications. The doppler principle is "wave –theory" that describes the relationship between velocity of the objects and transmitted or received wave frequencies **(Fujioka and Douville, 1992).**

The assessment of the extra-cranial cerebral vessels by doppler sonography was first reported by **Migaki and Kato in 1965 (Otis and Ringelstein, 1996).** Despite the rapid development of this technique extracranially, it was not applied to the intracranial arteries in that it was generally assumed that the cranium was largely impentratable to ultrasound. However in **1982, Aaslid, and Coworkers** developed a transcranial doppler device with a pulse sound emission of 2 MHz **(Pulsed doppler system)** that could penetrate the skull successfully at selected cranial foramina or thin regions of the skull and accurately measure both blood flow direction and velocities in the basal cerebral vessels and in the circle of Willis.

During the last several years, this technique has turned out to be an increasingly useful tool in the whole field of neurosonology, with the introduction of this intracranial ultrasound technique, it

becomes possible to record intracranial blood flow velocity directly. Thus, transcranial doppler become an important non-invasive method for assessing cerebral haemodynamics and for evaluating intracranial cerebral vascular disease.

In addition to its non-invasive character, TCD offers the advantages that relative changes in cerebral blood flow can be measured objectively immediately as often as desired and for as long as necessary **(Bishop et al., 1986).**

Principles of Transcranial Doppler:

Transcranial doppler, like extracranial doppler is based on the principle that signals emitted from an ulrasound source reflect off moving objects (**erythrocytes**) and the frequency of the reflected signal is shifted in direct proportion to the velocity of the moving object. Examination using continous-wave and pulse-wave doppler probes at 4 to 10 MHz frequencies has made possible accurate estimation of velocity and flow in extracranial arteries, but at this frequency range, attention of ultrasound waves by the skull resulted in weak reflections, making adequate recording of intracranial velocities impossible. So, lower frequencies (1 to 2 MHz) was introduced by **Aaslid and his collegues** and this enabled recording of blood velocities from the intracranial arteries **(Caplan et al., 1990).**

Methods of Transcranial Doppler Measurements:

Transranial doppler method uses a micro processor-controlled –directional pulse-wave adjustable probe that records range-gated trans-ducer measurements at selected depths inside the skull. These signals are recorded through the different skull windows. Analysis of fast-fourier-transformed doppler spectra allows display and calculation of peak systolic, peak diastolic and mean flow velocities **(Caplan et al., 1990).**

Newer equipments using a head piece with two scanning arms connected to the doppler probes allows the mapping of the sampled velocities as a color display of recorded spectra simultaneously in lateral, coronal and horizontal views. So, this technique facilitates the localization of the major cerebral arteries in 3 dimentions **(Caplan et al., 1990).**

Fundamental to the performance of a transcranial doppler examination, is a learned ability to maneuver the transducer so that the audible doppler signals with the highest pitch and strength (**i.e highest velocities and amplitudes**) are detected. The transducers applied are usually of low frequency (2.0-2.5MHz). The transducers applied are adjusted and angulated by the examiner, using knowledge about the anatomy and orientation of normal arteries, until maximum frequencies are obtained. Transcranial doppler takes advantage of specific areas of the cranium that have a

tendency to be relatively thin and natural foramina to gain access to the intracranial vasculature. There are three conventional regions of the skull through which the ultrasound beam is passed. These locations are referred to as **"acoustical windows"** and they include; the transtemporal window **(Aaslid et al., 1982),** the transorbital window **(Spencer and Whisler, 1986),** the suboccipital window **(Ringelstein et al., 1990)** and the submandibular window **(Otis and Ringelstein, 1996).**

The transtemporal acoustic window provides access to haemodynamic data from the middle, anterior and posterior cerebral arteries. In about 5% to 15% of individuals, satisfactory recordings from temporal windows can not be made. The frequency of absent temporal windows increases in the older age groups. A suboccipital approach, with inosonation through the foramen magnum provides access to the intracranial vertebral and basilar arteries. The transorbital approach can be used to inosonate the ophthalmic artery and carotid siphon via the optic foramen. These data allow evaluation of the direction, depth, speed and characteristics of flow in these vessels **(Ringelstein et al., 1990 and Tettenborn et al., 1990).**

The submandibular approach completes the examination in the sense that the retromandibular and moie distal, extradural parts of the internal carotid artery can be evaluated. This particular

examination is helpful as a complementary test to extracranial studies and helps to avoid overloading chronic occlusions of the internal Cortaid artery (ICA) in cases with abundant collateralization via the external carotid artery. The beam is directed slightly medially and posteriorly to the longitudinal axis of the body, where the ICA regularly can be tracked up to 80 to 85 mm, where it bends medio-anteriorly to form the siphon **(Otis and Ringelstein, 1996).**

Vessel Identification

The primary diagnostic measurements for identification of cerebral vessels relies on the acoustic windows used, insonation depth, flow direction at that depth, direction of transducer, flow velocities (**Mean time of flow velocity and systolic or diastolic peak flow velocities**), the traceability of the vessel segment, response to carotid compression (**Aaslid, 1987**) and characteristics of the doppler spectral pattern, in light of knowledge of normal anatomic and haemodynamic relationship (**Niederkorn et al., 1988**).

Table (3): Shows a summary of vessel identification criteria using free hand doppler techniques.

Artery	Transducer position	Depth of sample vol(mm)	Direction of flow	Mean velocity (cm /sec)	Response ipsilateral carotid compressions
MCA (M1)	Transtemporal	30-60	Toward	55 ± 12	Obliteration Diminishment
ACA (A1)	Transtemporal	60-80	Away	50±11	Obliteration Diminishment Reversal
PCA (P1)	Transtemporal	60-70	Toward	39±10	No change Augmentation
Carotid siphon sapraclinoid (Genu) parasellar	Transorbital	60-80	Away Bidirectional Toward	41 ± 11 47±14	Obliteration Reversal
VA	Transorbital	60-90	Away	38±10	—
BA	Transorbital	80-120	Away	41±10	—

(Fujioka and Douville, 1992).

MCA = Middle cerebral artery

ACA = Anterior cerebral artery

PCA = Posterior cerebral artery

VA = Vertebral artery

BA = Basilar artery

vol = volume

Carotid Compression Tests:

May be required for the unequivocal identification of certain arterial segments **(Ringelstein et al., 1990).** Compression tests during TCD examination can be performed on the common carotid arteries (CCA) low in the neck with two fingers or on the vertebral arteries at the mastoidal slope. Little risk of creating embolism from plaques in the carotid arteries exists if compression is performed only after knowledge of B-made imaging of the carotid arteries and by an experienced investigator **(Spencer and Whisler, 1986).**

The responses to carotid compression include no reaction at all; increase of flow velocity; decrease of flow velocity; reversal of flow and cessation of flow **(Otis and Ringelstein, 1996).**

Flow Velocity Measurements:

In normal subjects, the highest velocities are almost always found in the Middle cerebral artery (MCA) or anterior cerebral artery (ACA). The posterior cerebral arteries (PCAs) and the basilars have lower doppler shifts than the MCA. **(Fujioka and Douville, 1992).**

General trends are found in the flow velocities between the anterior and posterior circulations, so, we can identify the source of the audible doppler signal (MCA> ACA> PCA = BA= VA). This variation, however does not reflect differences in the ratios of

territorial blood flow and diameter of the feeding artery. Flow velocities in the basal cerebral arteries show a consistent decrease with increasing age **(Ringelstein et al., 1983).** These findings correlate well with age-related changes seen in studies of cerebral blood flow. This underlines the validity and sensitivity of the ultrasound methods as an intra-individually dose semiquantitative estimate of cerebral blood flow on the basis of velocity data **(Otis and Ringelstein, 1996).** Normal values have been established for flow velocity in each vessel segment **(Hennerici et al., 1987).**

Subjects and Methods

Subjects and Methods

This study included 52 children and adolescents. They were classified into the following groups.

Group I:

Thirty nine type-1 diabetic children and adolescents attending the Diabetes Clinic, Children's Hospital, Ain Shams University.

Patients in this group are subdivided into:

Group I A:

Thirteen patients having type-1 diabetes mellitus with duration less than five years. Their ages ranged between 9 and 17 years with a mean age of 14.54 ± 2.5 years. They were 7 males and 6 females.

Group I B:

Thirteen patients having type-1 diabetes mellitus, with duration ranging between 5 and 10 years. Their ages ranged between 11 and 18 years with a mean age of 14.53 ± 2.25. They were 7 males and 6 females.

Group I C :

Thirteen patients having type-1 diabetes mellitus for more than 10 years duration. Their ages ranged between 15.5 and 19 years with a mean age of 17.88 ± 1.19 years. They were 7 males and 6 females.

Group II:

Thirteen completely healthy children and adolescents. Their ages ranged between 6.5 and 19 years with a mean age of 10.92 ± 3.88. They were 7 males and 6 females.

All patients and controls were subjected to the following:

I- Full history taking, laying stress on duration of the disease, diabetic control, diabetic complications especially the cardiovascular complications, number of ketoacidosis attacks and neurological manifestations, also, careful history of drug intake, detailed family history of cardiovascular disease and diabetes mellitus.

II- Thorough clinical examination of patients and controls including assessment of anthropometeric measures: weight, height, and calculation of body mass index, cardiovascular examination and particular stress on neurological examination.

III- Fundus examination of both eyes.

IV- Plain X-ray chest, ECG and ECHO Cardiography if indicated.

V- Laboratory Investigations:

For both patients and controls the following laboratory tests were done :

1- Complete hemogram using coulter T 66.

2- Mean glycated hemoglobin% (HbA1c%) using Glyco Hb quick column procedure. Patients were considered to be under good metabolic control if HbA1c% was less than < 8% and were considered to be poorly controlled if HbA1c% ≥ 8%.

(Tietz, 1986)

3- Plasma viscosity by Oswald viscometer.

(Philips and Harkness, 1976)

4- Plasma fibrinogen level by hemostate fibrinogen kits.

(Dacie and Lewis, 1991)

5- Red cell deformability by study of RBCs filteration index.

(Buchan, 1980)

6- Assessment of serum lipid profile by chemical enzymatic method.

(Tietz, 1986)

VI- Transcranial-doppler ultrasound-acetazolamide test to study the blood flow velocity and vasoreactivity of the cerebral vessels by measuring blood flow velocity of the middle cerebral arteries (MCAs) before IVI of Acetazolamide and 15 minutes after its injection in a dose calculated as 10 mg / Kg for each subject or case.

- Each vial contains 500 mg dissolved in 5ml of distilled water.
- None of the subjects used any medications except insulin known to affect fibrinogen and lipoprotein metabolism. (e.g., B-blockers and thiazide diuretics).

Determination of Glycated Hemoglobin

Using Glyco Hb Quik column procedure*

Principle:

The Helena Glyco Hb Quik column method is a cation exchange chromatography method. The negatively charged resin in the column exhibits an affinity for the positively charged hemoglobin molecules. At a selected ionic strength and pH, the glycated hemoglobin is less positively charged than hemoglobin A and, therefore, binds to the negatively charged resin less tightly than Hb A. upon addition of the Glyco Hb developer to the column, Hb A_1 is eluted, while the other hemoglobin components are retained.

The Hb A_1, eluate is compared to the total fraction (TF) solution by determining the absorbance (Abs) of each using a spectrophotometer and then calculating the percentage of Hb A_1.

Specimen Collection:

1 ml of fresh whole blood was collected in tubes containing EDTA as an anticoagulant.

*Glyco Hb Quik column procedure provided by Helena laboratories, Beaumount, Texas, USA.

Procedure:

- 50 μL of well-mixed whole blood collect ed in EDTA was placed in test tube.
- 200 μL of Glyco Hb hemolysate reagent was added to the patient's sample.
- The tube was shaked to ensure complete hemolysis of the sample.
- The sample was allowed to stand for 10 minutes prior to use. Total volume of each sample preparation = 250 μL.
- The glyco Hb Quick column was prepared.
- 50μL of the hemolysate preparation was applied to the top of the column. The sample was allowed to soak into the resin completely.
- The glycated hemoglobin fraction was eluted by slowly adding 4.0 ml of Glyco Hb developer to the column.
- The Hb A_1% was determined in each sample using the Heme Spec plus photometer*.

Estimation of Total Cholesterol (TC):

- This was done using a colorimetric enzymatic method**.

*Heme Spec plus photometer provided by Helana Labrotories, Beaumont, Texas, U.S.A.

**DMA, Inc. Arlington, U.S.A.

Principle:

Cholesterol esters $\xrightarrow{\text{Cholesterol esterase}}$ cholesterol + F. acids

cholesterol + O_2 $\xrightarrow{\text{Cholesterol oxidase}}$ cholesten 4 one 3+ H_2O_2

2 H_2O_2+Phenol+amino-4antipyrine peroxidase → colored quinoneimine + 4 H_2O.

Reagents:

1- Enzymatic system:

- Sodium cholate	2.3 m mol / L
- Amino –4 antipyrine	0.25 m mol / L
- Peroxidase	1000 I U/ L
- Cholesterol oxidase	70 I U / L
- Cholesterol esterase	150 I U / L

2- Buffer : phosphate Buffer (pH 6.5) 100 m mol / L

- phenol	16 m mol /L

Procedure:

1- The content of one vial reagent (1) is poured into vial reagent 2.

2- They were mixed well and waited till total dissolution, and this reagent is stable for 5 months at 2-8°C.

3- It was pipetted into 3 test tubes:

	Test ml	Standard ml	Blank ml
Serum	0.1	-	-
Standard	-	0.01	-
Reconstituted reagent	1	1	1

4- They were mixed well and incubated for 5 minutes at 37°C.

5- The optical density of the test and standard were read against the Blank at 500 nm.

6- Calculation:

$$\text{Cholesterol} = \frac{\text{O.D"test"}}{\text{O.D."standard"}} \text{ x concentration "standard"}$$

- **Estimation of High Density Lipoprotein–Cholesterol (HDL-C):**

Technique:

Serum HDL-C was carried by precipitation*

Principle:

The chylomicrons and lipoprotein of very low density lipoproteins and low density lipoproteins contained in the sample were precipitated by the addition of phosphotungstic acid in the presence of magnesium ions.

*DMA, Inc. Arlington, U.S.A.

- The supernatant obtained after centrifugation contains high-density lipoproteins (HDL) from which HDL-C 'can be determined using cholesterol enzymatic color reagent.

Reagents:

Reagent I :

- Phosphotungstic acid	40 gm /L
- Magnesium choloride Mg Cl_2, 6 H_2O	100 gm /L
- pH	6.2

Reagent II:

- HDL –C calibrating solution:

Free + esterified cholesterol 1.3 m mol /L (50 gm /dl).

Procedure:

Precipitation : 500 µL of serum + 50µL of reagent (1) precipitant were mixed and litted stand for 10 minutes.

- They were centrifuged for 15 minutes at 5000 r.p.m.
- Determination of HDL-C as described above in the methodology for cholesterol measurement.

- **Estimation of Low- Density Lipoprotein –Cholesterol (LDL-C):**

The LDL–C of each sample was calculated by **Friedwald's formula.**

$$LDL - C = TC - (HDL - C + \frac{TG}{5})$$

- **Assay for Triglycerides (TG):**

Principle:

- This is a colorimetric enzymatic assay*.
- Triglycerides are triesters of fatty acids with glycerol.
- The present method employs microbial lipase to bring about rapid and complete hydrolysis of serum triglycerides.
- The glycerol produced undergoes a series of enzymatic reactions coupled in the final step to the reduction of tetrazollium salt producing a colored formazan.

Reagents:

1-Enzyme reagent : A lypholized reagent containing lipase, glycerol kinase (microbial), diaphorase (microbial), nicotene adenine dinucleotide (NAD), adenosine triphosphate and magnesium ion acetate.

1- The reagent is stable in the dry form until the data appearing on the label when stored refrigerated at (4-8^{o}C) and protected from light.

2- Reconstituting reagent: A buffered activator containing a stabilizer and preservative, stored refrigerated at 4-8^{o}C.

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*DMA, Inc. Arlington, U.S.A.

3- Triglycerides standard (200 mg /dL): A preserved solution containing glycerol in triolein and a stabilizer, stable until the date appearing on the label when stored refrigerated at 4-8 °C.

4- Working enzyme reagent: prepared when needed:

- 13 ml of reconstituting reagent were added to avial of enzyme reagent and mixed gently until complete dissolution occurs.
- This working enzyme reagent should not be freezed as this will denaturate some of the contained enzymes.

Procedure:

1- 1-2 ml of working enzyme was added to 0.02 ml of specimen and to a similar volume of standard.

2- The tubes were mixed and incubated for 10 minutes at 37°C.

3- Within the next 30 minutes, the photometer was set at 500 nm, zero adjustment with reagent blank.

4- The absorbencies of reference standard and each test specimen were determined, then serum triglycerides values were calculated using the following formulas.

$$\frac{\text{Absorbance of the test specimen}}{\text{Absorbance of the reference standard}} \times \text{conc of standard (200 mg /dL)}.$$

- **Determination of Fibrinogen:**

  Using hemostate fibrinogen*

*Dia Med AG, Switzerland.

Test Principle:

The hemostate. fibrinogen test is based on the most commonly used method by the addition of an optimal amount of bovine thrombin which is added to the 1 : 10 prediluted sample plasma. The measured clotting time is inversely related to the fibrinogen concentration in the specimen.

Specimen Collection and Processing:

- Anticoagulant: 3.2% (0.109 M) sodium citrate was used for coagulation assay.

An exact ratio of nine parts blood to one part citrate was used (1.8cc blood was added to a tube containing 0.2 cc sodium citrate).

- Centrifugation : 10 minutes at 2.500 gm.
- Plasma storage : 8 hours at 20°C.
- Plasma should be diluted 1 : 10 with imidazole buffered saline prior to use : 0.9 ml imidazole buffered saline was added to 0.1 ml plasma and mixed (this equals a 1 : 10 dilution).

Test Procedure:

0.2 ml of the diluted samples, reference or control was incubated for 4-6 minutes at 37°C then we added 0.1 ml of fibrinogen reagent and started the timer simultaneously. The time required for clot formation was recorded.

The fibrinogen level was determined by enclosed conversion label. For clotting times below 8 sec. A 1: 20 dilution, above 25

sec. A 1: 5 or 1: 3 dilution was done. For calculating the fibrinogen concentration, the appropriate dilution factor was used.

- **Measurement of the Red Cell Deformability:**

It was done using red cell filtration index technique

Apparatus: The apparatus, as illustrated in figure (8), was prepared. The experimental method and sample handling were identical to the methodology of **Buchan (1980)** in the evaluation of whole blood filtration method. Nucleopore 5 μm pore diameter filter membranes were used (Sterlin Ltd., Teddington, Meddlesex, TWII 8QZ).

Sample Handling:

1- Venous blood was drawn into clean disposable syringes with minimal venous occlusion.

2- Each sample was anticoagulated with EDTA 1.5 mg/ml of blood.

3- The sample was centrifuged at 2000 gravity for 15 minutes, then the plasma was separated.

4- The buffy white coat was aspirated and discarded.

5- The erythrocytes were then resuspended in their native plasma to give a packed cell volume of between 0.15 and 0.20.

6- The sample was stored at room temperature until measurement, which was then completed within 2 hours of venipuncture.

7- The one ml. Volume of resuspended RBCs was allowed to pass and the time consumed calculated by stopwatch then

erythrocyte filtration rate was calculated as the volume of erythrocytes passing through a 5 mm pore filter in one minute under a perfusion pressure of 20 cm H_2O.

8- The sample and the apparatus were kept in an incubator at 37°C for 10 minutes prior to measurement in order to standardize the measurement temperature.

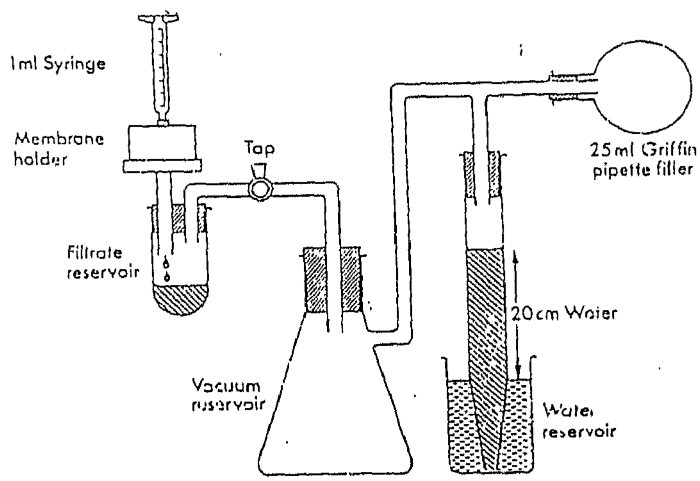


Figure (8): Diagrammatic representation of the red cell filtration index technique apparatus.

- **Measurement of Plasma Viscosity:**

- It was done using the classic Oswald-U-tube viscometer.
- The principle underlying capillary tube viscometer is the measurement of time taken for a standard volume of test tube fluid to flow through a capillary tube of standard length and diameter under a standard force and at standard temperature usually 35°C, 25°C and 4°C.
- In the classic Oswald-U-tube viscometer, the driving force is the standard height of the test fluid itself and the viscosity measured is named kinematic viscosity.
- Other capillary instruments have an independent driving force and produce absolute or dynamic viscosity measurements.
- Capillary viscometers are suitable for measurements of plasma or serum viscosity.
- In some laboratories, the time required for a constant volume of fluid to flow through the viscometer tube is compared to the flow rate of water.
- The relative viscosity of serum obtained is measured as the flow time of serum divided by the flow time of water.

- **Transcranial Doppler Ultrasonography (TCD):**

- **Equipment:** Figures (9 & 10):

TCD equipment used was manufactured by trans-scan*"

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*Eden Medical Electronic Gmblt (West Germany).

which is a 3-dimensional transcranial doppler scanner. The trans-scan system 3 D-transcranial doppler scanner incorporates an AT compatible computer, 2, 4, 8 MHz pulsed doppler ultrasound, real time sliding average FFT spectrum analysis, sophisticated soft ware programs and the exclusive trans-scan head piece with position sensing transducers.

With this system, it is possible to quantify and document the position of the Doppler sample volume, in three orthogonal planes, within the cranial space. Using this sample volume position documentation technique to locate and record multiple intracranial doppler spectra, a multi-projection color-coded, transcranial flow image of the circle of Willis and its branches can be produced.

The trans-scan system is supplied with five ultrasonic transducers (probes). Two transducers are incorporated in the scanning head piece, three are designed to operate as hand-held transducers. The transducers located in the scanning head piece are 2 MHz pulsed doppler transducers. They are used individually to produce the transcranial flow images and operate only in the ON-line scan mode. The three hand held pulsed doppler transclucers have operating frequencies of 2,4 and 8 MHz. The sample volume size (pulsed burst width) of each transducer can be adjusted to best suit the application. The hand-held doppler transducer function only in the ON-line hand held mode.

A standard AT computer keyboard is supplied with the trans-scan system in addition to a mechanical mouse operating the mouse systems PC paint plus graphics programs. A remote control unit and a high resolution (640 dots x 350 lines) RGB computer monitor are also supplied with trans-scan system.

- Examination Techniques of TCD:

There are two prerequisites to be fulfilled before performing a TCD examination:

1- The states of the extra-cranial arteries must be known completely.

2- The patient must be resting comfortably to avoid major fluctuations of PCO_2 and movements artifacts.

In addition, two anatomic considerations must be dealt with by the examiner:

1- The number and accessibility of the ultrasonic windows or foramina within the skull that can be penetrated with the ultrasonic beam are often limited and / or not easily identified.

2- The arteries at the base of the skull vary greatly in respect to size, course, development, and site of access.

- Ultrasonic Windows:

There are four different TCD approaches have been described to insonate the intracranial arteries: the transtemporal, transorbital, suboccipital and submandibular approaches, Figure (11).

In the temporal approach; the probe is placed on the temporal aspect of the head, cephalad to the zygomatic arch, and immediately anterior and slightly superior to the tragus of the ear concha. Using these transtemporal approaches, the beam can be angulated anteriorly or posteriorly relative to the corresponding probe positions on the opposite side of the head.

The anterior orientation of the beam allows for the insonation of the MI and M2 segments of the middle cerebral artery (MCA). The CI segment of carotid siphon (CS), and the AI Segment of the anterior cerebral artery (ACA). The posteriorly angulated beam insonates the P_1 and P_2 segments of the posterior cerebral artery, Figure (12).

The transtemporal approach can show the components of the anterior cerebral circulation may be evaluated by placing the transducer against the closed eyelid. The ophthalmic artery can be insonated through this window. Also, the proximal part of the internal carotid artery is insonated through this window, Figure (13).

The suboccipital approach is essential for screening the vertebral and basilar arteries throughout their entire length. The probe is placed exactly between the posterior margin of the

foramen magnum and the palpable spinous process of the first cervical vertebra Figure (14).

The submandibular approach Figure (15)..

- **Vasoreactivity Testing:**

After the mean flow velocities of both carotid vessels and vertebro basilar vessels are recorded. Then, we test for vasomotor reactivity by the use of Acetazolamide (Diamox) which is a carbonic anhydrase inhibitor 500 mg vial dissolved in 5 ml of distilled water and injected IV in a dose of 10 mg/Kg while the patient lying supine and relaxed.

Then the patient was left for 15 minutes, then we repeat again the TCD examination through the same windows, and record the flow velocities in the MCAs ACA, ICA and vertebrobasilar arteries.

Normally the use of Acetazolamide (Diamox) will result in an increase of at least 30% in the flow velocities. Impaired vasoreactivity was considered if the increase of the mean flow velocities is less than 30% of the mean flow velocity of the vessel.

$$CVR = \frac{VMCA_{AZ} - VMCA_{rest}}{VMCA_{rest}} x100$$

(Fulsedi et al., 1997).

Anthropometric measures:

- Height was measured using Holtain Limited (Made in Britain – Crymych, Dyfed).
- Weight was measured using Weight minder (Metro. Co.).
- Body mass index (BMI):

$$BMI = \frac{\text{Body weight (Kg)}}{\text{Standing height}^2\ (m^2)} = Kg/m^2$$

(Bray, 1978)

Statistical Methods:

Mean value and standard deviations were calculated for each variable examined according to the equations:

Arithematic mean $\overline{X} = \frac{\in \overline{x}}{n}$

Standard deviation $S.D. = \sqrt{\frac{\varepsilon(\overline{x}_1 - \overline{x}_2)^2}{n-2}}$

To test the significance of difference between means of 2 different groups, student's "t" test was applied

$$"t" = \frac{\overline{x}_1 - \overline{x}_2}{\sqrt{\frac{SD_1^2}{n_1} + \frac{SD_2^2}{n_2}}}$$

where:

$\overline{x}_1$ = Mean of the first group

$\overline{x}_2$ = Mean of the second group

SD_1 = Standard deviation of the first group

SD_2 = standard deviation of the second group.

N_1 = Size of samples in the first group.

N_2 = Size of samples in the second group.

"t" was calculated and compared with tabulated "t" at degree of freedom = $(n_1 + n_2)-2$ where : $P > 0.05$ is not significant.

$P < 0.05$ is significant.

Correlation between variables of different groups were estimated using the correlation coefficient = "r"

$$"r" = \frac{Co\ var.xy}{\sqrt{Co\ var\ x \quad x \quad Co \quad var.y}}$$

where :

$$Co\ var\ x = \sum x^2 = \frac{(\sum X)^2}{n}$$

$$Co\ var\ y = \sum y^2 = \frac{(\sum y)^2}{n}$$

$$Co\ var\ Xy = \sum X - y = \frac{\sum X \quad x \quad \sum y}{n}$$

"r" is calculated and compared with tabulated "r" at degree of freedom = n –2

Where :

$P > 0.05$	is not significant
$P < 0.05$	is significant

* Statistics were obtained from **Pepkin. (1984).**



Figure (9): Photographic illustration of TCD apparatus

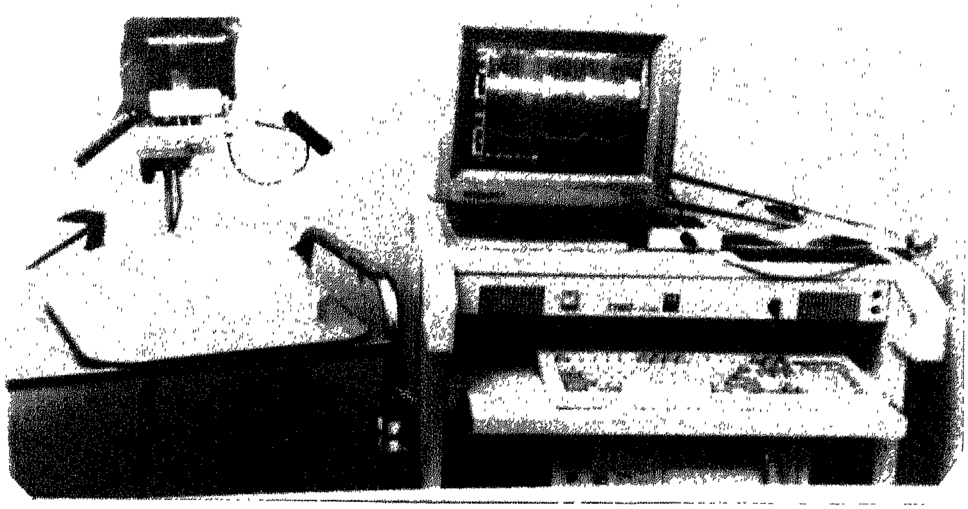


Figure (10): Photographic illustration of TCD apparatus

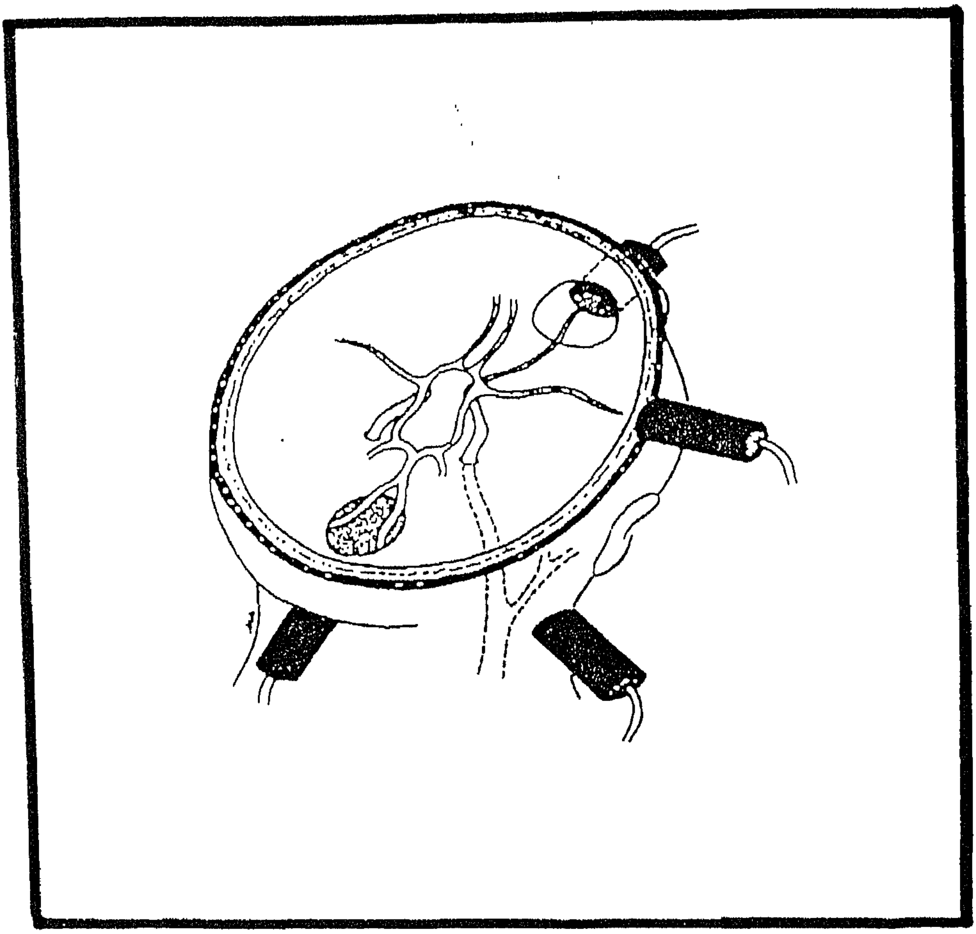


Figure (11): Relationship of ultrasonic probes to the available ultrasound windows and to the basal cerebral arteries.

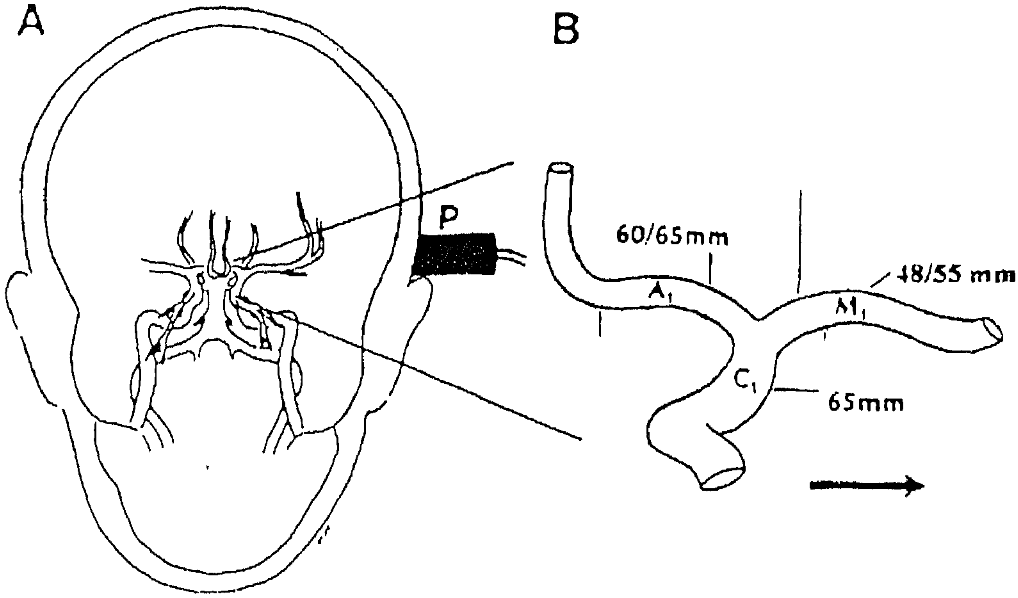


Figure (12-a): Transtemporal Approach; for examination of MCA, ACA and internal carotid artery bifurcation.

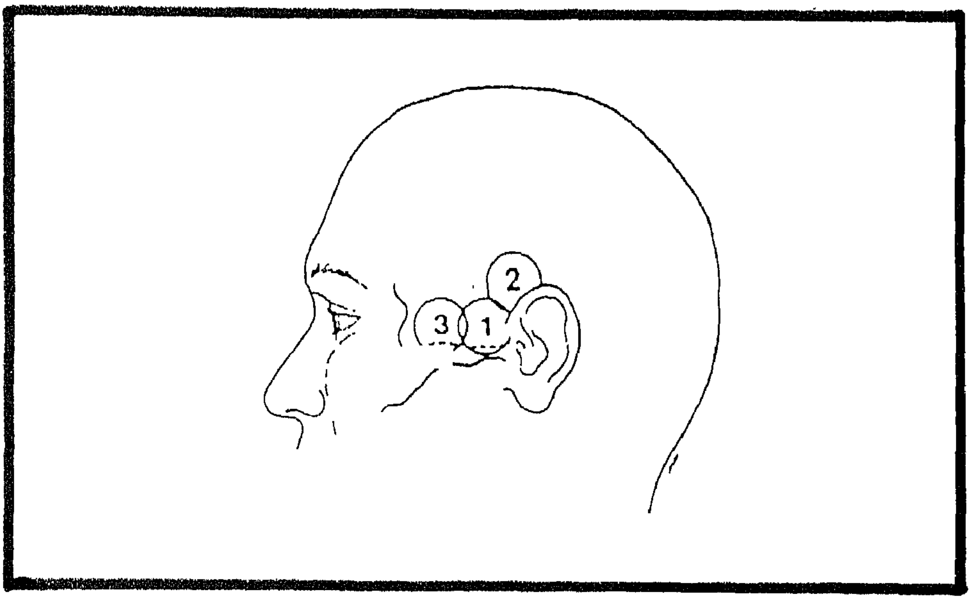


Figure (12-b): Available temporal ultrasonic windows and probe placement.
1, Preauricular position. 2, Posterior window, 3, Anterior window.

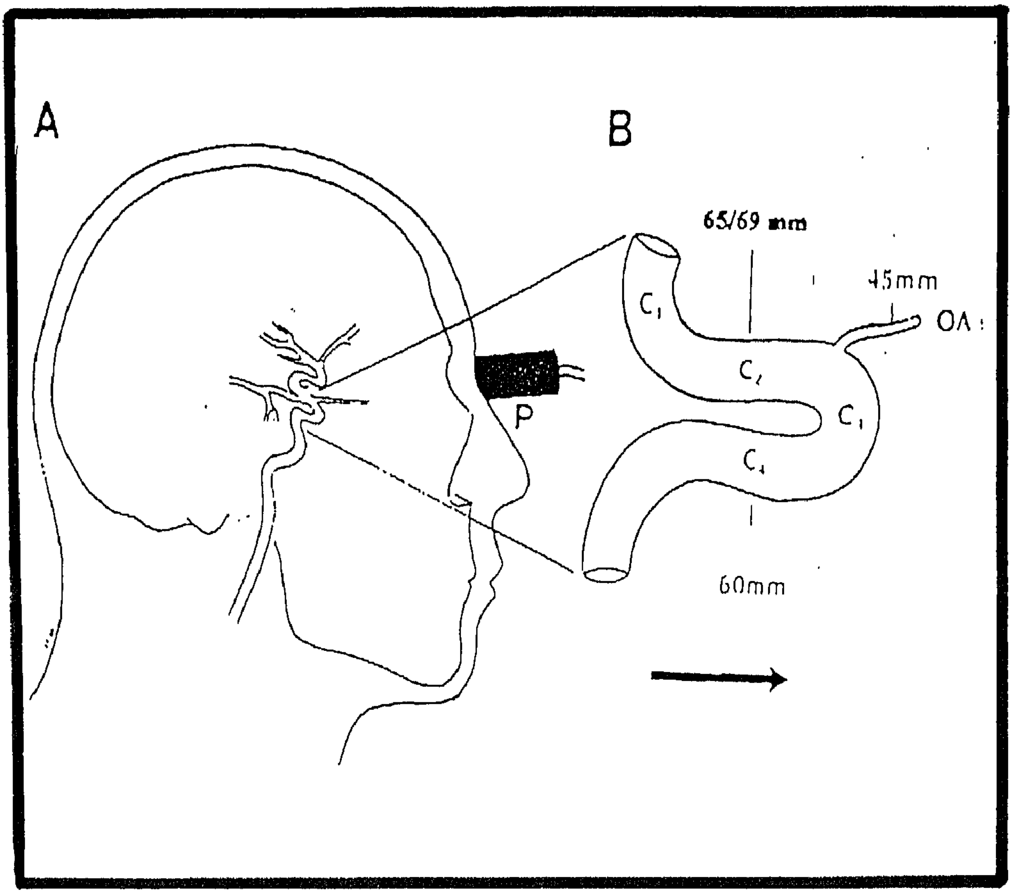


Figure (13): Transorbital approach; for the insonation of the ophthalmic artery and carotid siphon.
A, probe (P) location and relationship to the ophthalmic artery and carotid siphon.
B, representative insonation depths within various segments of carotid siphon (C1 C4) and ophthalmic artery (OA).

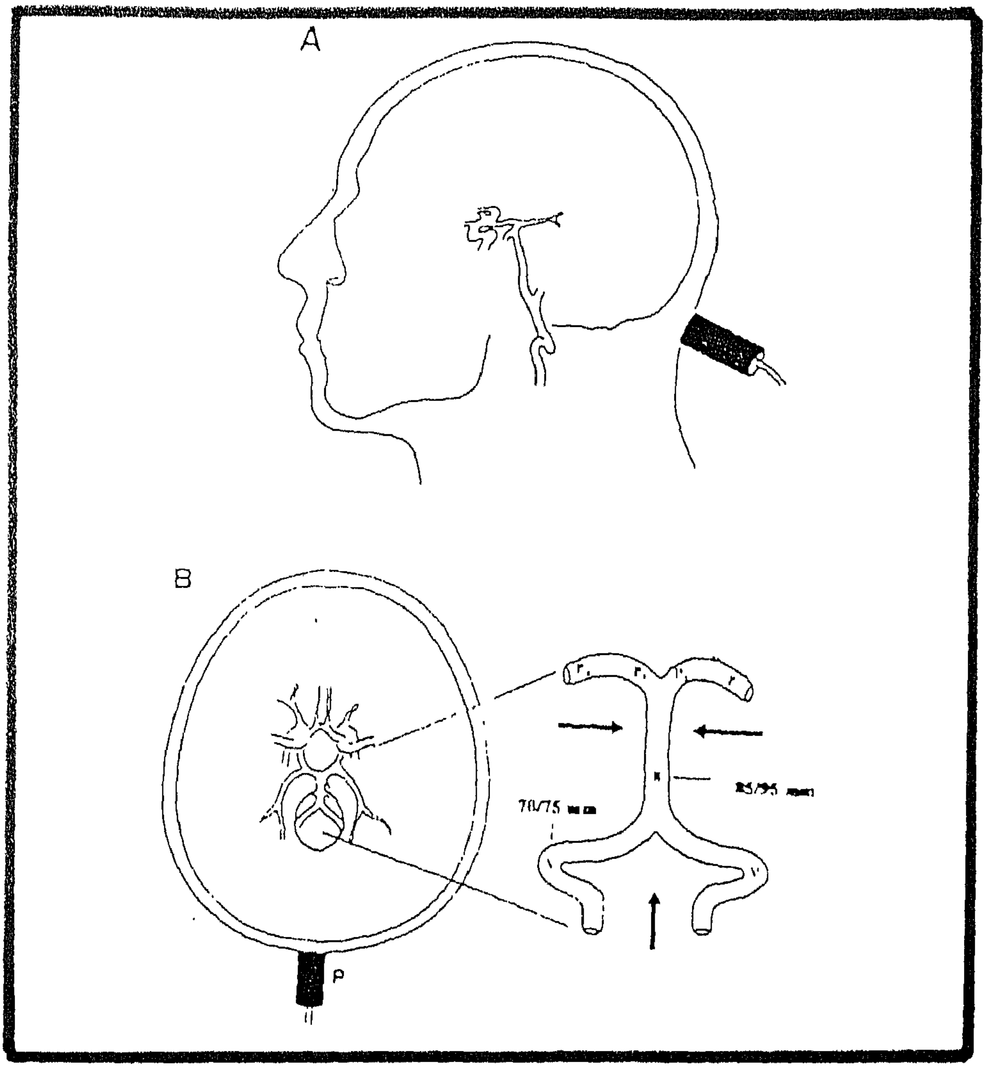


Figure (14): A, Suboccipital Approach; for examination of the vertebral system.
B, Representative insonation depths within the distal vertebral arteries (VA) and the basilar trunk (B).

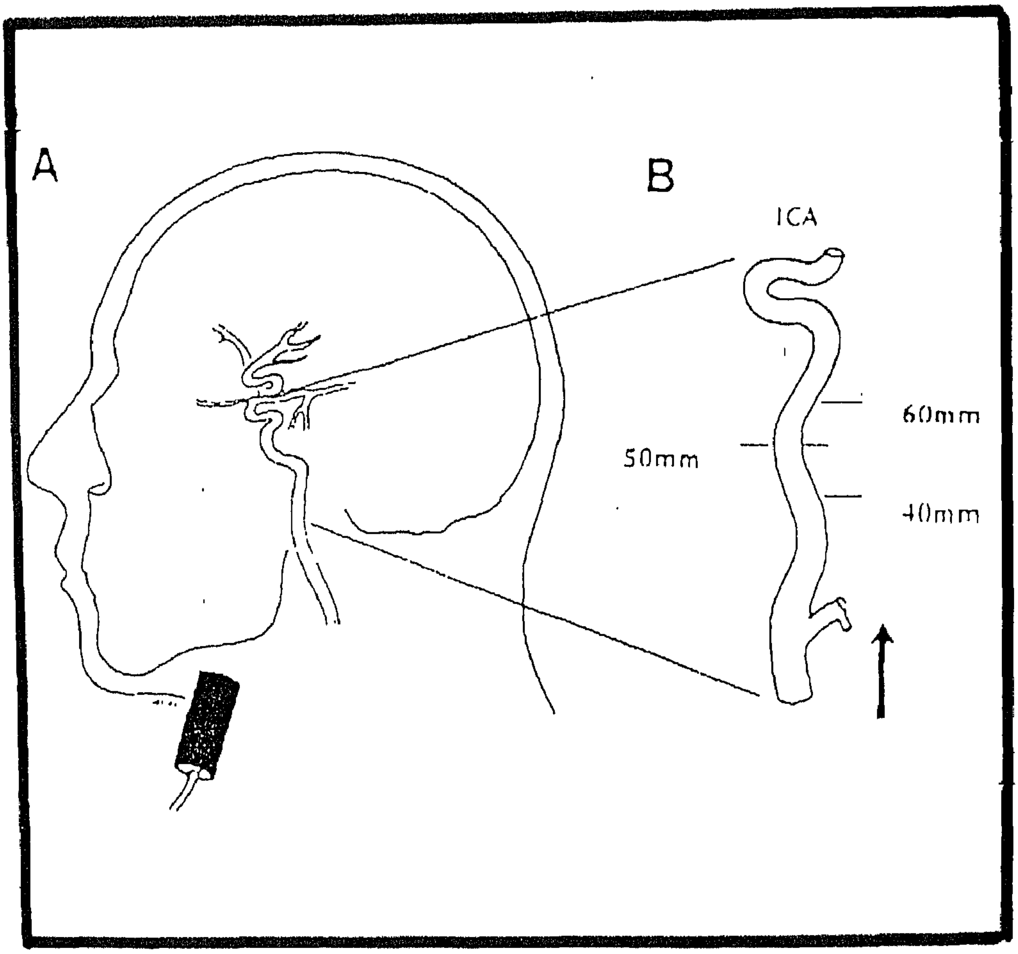


Figure (15): A, Submandibular approach; for examination of the petrous (distal) portion of the internal carotid artery (ICA).
B, Representative insonation depths within the distal intracranial ICA.

Results

The results of the current study are represented in the following tables and figures.

Table (4): Comparative study of hematocrit % (Hct%) value and glycated hemoglobin % (HbA1c%) in group IA and control group.

Group / Variable	Group IA n = 13 $\bar{X} \pm$ S.D	Controls n = 13 $\bar{X} \pm$ S.D	"t" test	"p" value
Hematocrit % (Hct %)	37.55 ± 3.62	39.35 ± 2.07	1.55	> 0.05*
Glycated Hb% (HbA1c %)	8.4 ± 0.93	7.15 ± 0.55	4.17	< 0.001***

n = Number

$\bar{X}$ = Mean

S.D = Standard deviation.

* = Non significant.

*** = Highly significant

Table (5): Comparative study of lipid profile in group IA and control group.

Group / Variable	Group IA n = 13 $\bar{X} \pm S.D$	Controls n = 13 $\bar{X} \pm S.D$	"t" test	"p" value
TC mg/dL	214.85±46.85	171.69±24.35	2.95	< 0.01***
HDL-C mg /dL	50.38 ± 8.88	66.07 ± 3.92	5.83	< 0.001***
LDL-C mg/dL	139.76± 46.10	87.69 ± 31.17	3.37	< 0.001***
TG mg/dL	123.31± 48.8	88 ± 27.88	2.26	< 0.05**

n = Number $\bar{X}$ = Mean

S.D. = Standard deviation.

TC = Total cholesterol TG = Triglycerides

HDL-C = High density lipoprotein –cholesterol

LDL-C = Low density lipoprotein cholesterol

** = Significant.

*** = Highly significant.

Table (6) : Comparative study of rheological data in group IA and control group.

Group / Variable	Group IA n = 13 $\overline{X} \pm S.D$	Controls n = 13 $\overline{X} \pm S.D$	"t" test	"p" value
Plasma Viscosity	1.17 ± 0.10	1.138±0.09	0.85	> 0.05*
RBCs Deformability	2.10 ± 0.17	2.32±0.46	1.61	> 0.05*
Fibrinogen gm/ dL	2.08 ± 0.42	2.07±0.27	0.072	> 0.05*

n = Number

$\overline{X}$ = Mean

S.D. = Standard deviation

* = Non significant.

RBCs = Red blood cells

Table (7) : Comparative study of MFVs of MCAs before and 15 minutes after Diamox injection and mean of vasoreactivities % in group IA and control group.

Group / Variable	Group IA n = 13 $\bar{X}$ ± S.D.	Controls n = 13 $\bar{X}$ ± S.D.	"t" test	"p" value
MFVs of MCAs before Diamox injection cm /sec	71.61±11.31	76.46±3.04	1.49	> 0.05*
MFVs of MCAs after Diamox injection cm /sec	97.11± 14.53	103.07±3.52	1.43	> 0.05*
Mean of vasoreactivities%	37.81±5.33	34.58±5.42	1.53	> 0.05*

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

MCAs = Middle cerebral arteries

* = Non significant.

Table (4) and figures (16 & 17): show statistical comparison of hematocrit % (Hct%) and glycated hemoglobin % (HbA1c%) between type-1 diabetics of a disease duration less than 5 years (group IA) and control group.

It is clearly demonstrated that, the mean value of hematocrit% (Hct%) showed no statistically significant difference in patients compared to its mean value in control group being 37.55 ± 3.62% in group IA and 39.35 ± 2.07 % in the control ($P > 0.05$), table (4) and figure (16). The mean value of glycated hemoglobin% (HbA1c %) was significantly high in diabetics compared to its mean value in controls, being, 8.40 ± 0.93 in patients and 7.15 ± 0.55 % in controls. ($P < 0.001$), table (4) and figure (17).

Table (5) and figures (18 & 19 & 20 & 21): show statistical comparison of lipid profile between type-1 diabetics of a disease duration less than 5 years (group IA) and control group.

The mean serum TC was significantly high in diabetic patients compared to its mean value in controls, being 214.85 ± 46.85 mg / dL in patients and 171.69 ± 24.35 mg /dL in controls. ($P < 0.01$), table (5) figure (18). On the other hand, the mean serum HDL-C was significantly low in patients compared to its mean value in control group being, 50.38 ± 8.8 mg/dL in patients and 66.07 ± 3.92 mg/dl in controls ($P < 0.01$). table (5) and figure (19). But, the mean serum LDL-C was significantly high in patients

compared to its mean value in controls being 139.76 ± 46.10 mg/dL in group IA and 87.69 ± 31.17 mg/dL in controls. (P < 0.001), table (5) and figure (20). At the same time, the mean serum TG was significantly high in patients compared to its mean value in controls, being 123.31 ± 48.8 mg/dL in patients and 88 ± 27.88 mg / dL in the control group.(P < 0.05), table (5) and figure (21).

Table (6) and figures (22 & 23 & 24): show statistical comparison of rheological parameters between type-1 diabetics of a disease duration less than 5 years (group IA) and control group.

The mean value of plasma viscosity showed no statistically significant difference in diabetics compared to its mean value in controls, being 1.17 ± 0.10 in patients and 1.138 ±0.09 in controls. (P > 0.05), table (6) and figure. (22). Also, the mean value of RBCs deformability showed no statistically significant difference in diabetics compared to its mean value in controls, being, 2.10 ± 0.17 in patients and 2.32 ± 0.46 in controls. (P> 0.05) , table (6) and figure (23). At the same time, the mean value of serum fibrinogen showed no statistically significant difference in patients compared to its mean value in controls, being 2.08 ± 0.42 gm / dL in patients and 2.07 ± 0.27 gm / dl in controls. (P > 0.05), table (6) and figure (24).

Table (7) and figures (25 & 26 & 27): show statistical comparison of the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At

rest) and 15 minutes after its injection and mean of vasoreactivities% between diabetics of a disease duration less than 5 years (group IA) and control group.

The mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) showed no statistically significant difference in patients compared to its mean value in controls, being 71.61 ± 11.31 cm/sec in patients and 76.46 ± 3.04 cm /sec in controls. (P > 0.05), table (7) and figure. (25). Also, the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection showed no statistically significant difference in patients compared to its mean value in controls being 97.11 ± 14.53 cm / sec in patients and 103.07 ± 3.52 cm / sec in controls. (P > 0.05), table (7) and figure. (26). Also, the mean value of mean of vasoreactivties % showed no statistically significant difference in diabetic patients compared to its mean value in controls, being 37.81 ± 5.33% in patients and 34.58 ± 5.42 % in the controls. (P > 0.05), table (7) and figure. (27).

Table (8) : Comparative study of hematocrit % (Hct%) value and glycated hemoglobin% (HbA1c%) in group IB and control group.

Group / Variable	Group IB n = 13 $\bar{X}$ ± S.D.	Controls n = 13 $\bar{X}$ ± S.D.	"t" test	"p" value
Hematocrit % (Hct %)	38.89±2.72	39.35±2.07	0.68	$> 0.05^{*}$
Glycated Hb% (HbA1c%)	8.66±1.04	7.15± 0.55	4.62	$< 0.001^{***}$

n = Number.

$\bar{X}$ = Mean.

S.D = Standard deviation.

* = Non significant.

*** = Highly significant.

Table (9) : Comparative study of lipid profile in group IB and control group.

Group / Variable	Group IB n = 13 $\bar{X} \pm S.D.$	Controls n = 13 $\bar{X} \pm S.D.$	"t" test	"p" value
TC mg /dL	198.38±71.39	171.69±24.35	1.28	>0.05*
HDL-C mg/dL	46.76±5.65	66.07±3.92	10.11	< 0.001***
LDL-C mg/dL	126.38±68.46	87.69±31.17	1.85	< 0.05**
TG mg/ dL	123.15±39.76	88±27.88	2.61	< 0.01***

n = Number $\bar{X}$ = Mean

S.D. = Standard deviation

TC = Total cholesterol TG = Triglycerides

HDL-C = High density lipoprotein cholesterol

LDL-C = Low density lipoprotein cholesterol

* = Non significant

** = Significant

*** = Highly significant

Table (10) : Comparative study of rheological data in group IB and control group.

Group / Variable	Group IB n = 13 $\bar{X} \pm S.D$	Controls n = 13 $\bar{X} \pm S.D$	"t" test	"p" value
Plasma viscosity	1.6 ± 0.12	1.138 ± 0.09	11.10	< 0.001***
RBCs Deformability	1.44 ± 0.17	2.32 ± 0.46	6.44	< 0.001***
Fibrinogen gm /dL	3.07± 0.63	2.07 ± 0.27	5.23	< 0.001***

n = Number.

$\bar{X}$ = Mean.

S.D = Standard deviation.

*** = Highly significant.

RBCs = Red blood cells.

Table (11) : Comparative study of MFVs of MCAs before and 15 minutes after Diamox injection and mean of vasoractivities% in group IB and control group.

Group / Variable	Group IB n = 13 $\bar{X} \pm$ S.D	Controls n = 13 $\bar{X} \pm$ S.D	"t" test	"p" value
MFVs of MCAs before Diamox injection cm /sec	65.42 ± 9.98	76.46 ± 3.04	3.81	< 0.001***
MFVs of MCAs after Diamox injection cm /sec	80.42±12.90	103.07 ± 3.52	6.108	< 0.001***
Mean of vaso-reactivates %	22.88 ± 5.09	34.58 ± 5.42	5.67	< 0.001***

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

MFVs = Mean flow velocities

MCAs = Middle cerebral arteries.

*** = Highly significant

Table (8) and figures (16 & 17): show statistical comparison of hematocrit % (Hct%) and glycaeted hemoglobin % (HbA1c%) between type-1 diabetics of a disease duration ranging between 5 and 10 years (group IB) and control group.

The mean value of hematocrit% (Hct%) showed no statistically significant difference in patients compared to its mean value in control group being 38.89 ± 2.72% in group IB and 39.35 ± 2.07 % in the controls. (P > 0.05), table (8) and figure (16). On the other hand, the mean value of glycated hemoglobin % (HbA1c %) was significantly high in patients compared to its mean value in controls being, 8.66 ± 1.04 in group IB and 7.15 ± 0.55 % in controls group. (P < 0.001), table (8) and figure (17).

Table (9) and figures (18 & 19 & 20 & 21): show statistical comparison of lipid profile between type-1 diabetics of a disease duration ranging between 5 and 10 years (group IB) and control group.

The mean serum TC showed no statistically significant difference in patients compared to controls being 198.38 ± 71.39 mg/dL in diabetics and 171.69 ± 24.35 mg/ dL in the controls. (P > 0.05), table (9) and figure (18).

On the other hand, the mean serum HDL-C was significantly low in patients compared to its mean value in controls being, 46.76 ± 5.65 mg/dL in diabetics and 66.07 ± 3.92 mg/dL in controls. (P < 0.001), table (9) figure (19). However, the mean serum LDL-C was significantly high in patients compared to controls being 126.38 ± 68.46 mg/dL in patients and 87.69 ± 31.17 mg/dL in controls. (P < 0.05), table (9) and figure. (20). Also, the mean serum TG was significantly high in patients compared to controls, being 123.15±39.76 mg/dL in patients and 88 ±27.88 mg/dL in control. (P < 0.01), table (9) and figure. (21).

Table (10) and figures (22 & 23 & 24): show statistical comparison of rheologoical parameters between type-1 diabetics of a disease duration ranging between 5 and 10 years (group IB) and controls.

The mean value of plasma viscosity was significantly high in patients compared to controls, being 1.6 ± 0.12 in patients and 1.138± 0.09 in controls. (P < 0.001), table (10) and figure (22).
On the other hand, the mean value of RBCs deformability was significantly low in patients compared to controls, being, 1.44 ± 0.17 in patients and 2.32 ±0.46 in controls. (P< 0.001), table (10) and figure (23). But, the mean serum fibrinogen was significantly high in patients compared to controls being 3.07±0.63

gm/dL in patients and 2.07 ± 0.27 gm / dL in controls. ($P < 0.001$), table (10) and figure (24).

Table (11) and figures (25 & 26 & 27) : show statistical comparison of the mean value of mean flow velocities of middle cerebral arteries, (MFVs of MCAs) before and 15 minutes after Diamox injection and mean of vasoreactivities between type-1 diabetics of a disease duration ranging between 5 and 10 years (group IB) and control group.

The mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) was significantly low in patients compared to controls, being 65.42 ± 9.98 cm / sec in patients and 76.46 cm/sec in controls. ($P < 0.001$), table (11) and figure (25). Also, the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection was significantly low in patients compared to the controls being 80.42 cm / sec in patients and 103.07cm /sec in controls. ($P < 0.001$), table (23) and figure (26).At the same time, the mean value of mean of vasoreactivities% was significantly low in patients compared to controls being 22.88 ± 5.09 in patients and 34.58 ± 5.42 in the controls. ($P< 0.01$), table (11) and figure (27).

Table (12) : Comparative study of hematocrit % (Hct%) value and glycated hemoglobin % (HbA1c%) in group IC and control group.

Group / Variable	Group IC n = 13 $\bar{X}$ ± S.D.	Controls n = 13 $\bar{X}$ ± S.D.	"t" test	"p" value
Hematocrit % (Hct %)	39.48±2.71	39.35±2.07	0.05	> 0.05*
Glycated Hb% (HbA1c%)	9.05±0.58	7.15± 0.55	8.57	< 0.001***

n = Number.

$\bar{X}$ = Mean.

S.D. = Standard deviation.

* = Non significant.

*** = Highly significant.

Table (13) : Comparative study of lipid profile in group IC and control group.

Group / Variable	Group IC n = 13 $\overline{X} \pm$ S.D.	Controls n = 13 $\overline{X} \pm$ S.D.	"t" test	"p" value
TC mg /dL	249.61±59.22	171.69±24.35	4.39	<0.001***
HDL-C mg/dL	47.38± 3.04	66.07±3.92	13.57	< 0.001***
LDL-C mg/dL	172.53±54.96	87.69 ± 31.17	4.84	< 0.001***
TG mg/dL	147.46±59.87	88±27.88	3.25	< 0.01***

n = Number

$\overline{X}$ = Mean

S.D. = Standard deviation

TC = Total cholesterol

TG = Triglycerides

HDL-C = High density lipoprotein cholesterol

LDL-C = Low density lipoprotein cholesterol

*** = Highly significant

Table (14) : Comparative study of rheological data in group IC and control group.

Group / Variable	Group IC n = 13 $\bar{X} \pm S.D.$	Controls n = 13 $\bar{X} \pm S.D.$	"t" test	"p" value
Plasma viscosity	1.89±0.23	1.138 ± 0.09	10.97	< 0.001***
RBCs Deformability	1.35±0.11	2.32 ± 0.46	7.35	< 0.001***
Fibrinogen gm /dL	4.16 ± 1.08	2.07 ± 0.27	6.76	< 0.001***

n = Number.

$\bar{X}$ = Mean.

S.D. = Standard deviation.

*** = Highly significant.

RBCs = Red blood cells.

Table (15) : Comparative study of MFVs of MCAs before and 15 minutes after Diamox injection and mean of vasoractivities% in group IC and control group.

Group / Variable	Group IC n = 13 $\bar{X} \pm S.D.$	Controls n = 13 $\bar{X} \pm S.D.$	"t" test	"p" value
MFVs of MCAs before Diamox injection cm/sec	64.46±10.51	76.46±3.04	3.95	$< 0.001^{***}$
MFVs of MCAs after Diamox injection cm/sec	73.30±12.07	103.07 ± 3.52	8.53	$< 0.001^{***}$
Mean of vaso-reactivates %	13.44 ± 8.84	34.58 ± 5.42	7.36	$< 0.001^{***}$

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

MFVs = Mean flow velocities

MCAs = Middle cerebral arteries.

*** = Highly significant

Table (12) and figures (16 & 17): show statistical comparison of hematocrit% (Hct%) and glycated hemoglobin % (HbA1c%) between type-1 diabetics of a disease duration more than 10 years (group IC) and control group.

The mean value of hematocrit% (Hct%) showed no statistically significant difference in patients compared to controls being 39.48 ± 2.71 % in patients and 39.35 ± 2.07 % in controls. (P > 0.05), table (12) and figure (16). On the other hand, the mean value of glycated hemoglobin% (HbA1c%) was significantly high in patients compared to controls, being, 10.05 ± 0.58 % in patients and 7.14 ± 0.55 5 in controls. (P< 0.001), table (12) and figure (17).

Table (13) and figures (18 & 19 & 20 & 21): show statistical comparison of lipid profile between type-1 diabetics of a disease duration more than 10 years and control group.

The mean serum TC was significantly high in patients compared to controls, being, 249.61 ± 59.22 mg /dl in patients and 171.69 ± 24.35 mg/dL in controls. (P < 0.001), table (13) and figure (18). But, the mean serum HDL-C was significantly low in patients compared to controls being 47.48 ±3.04 mg/dL in patients and 66.07 ± 3.92 mg /dL in controls. (P< 0.01), table (13) and figure (19). On the other hand, the mean serum LDL-C was

significantly high in patients compared to controls being, 172.53 ± 54.96 mg/dL in patients and 87.69 ± 31.17 mg/dL in controls. ($P < 0.001$), table (13) and figure (20). Also, the mean serum TG was significantly high in patients compared to controls, being 147.46 ± 59.87 mg/dL in patients and 88 ± 27.88 mg/dL in controls. ($P < 0.01$), table (13) and figure (21).

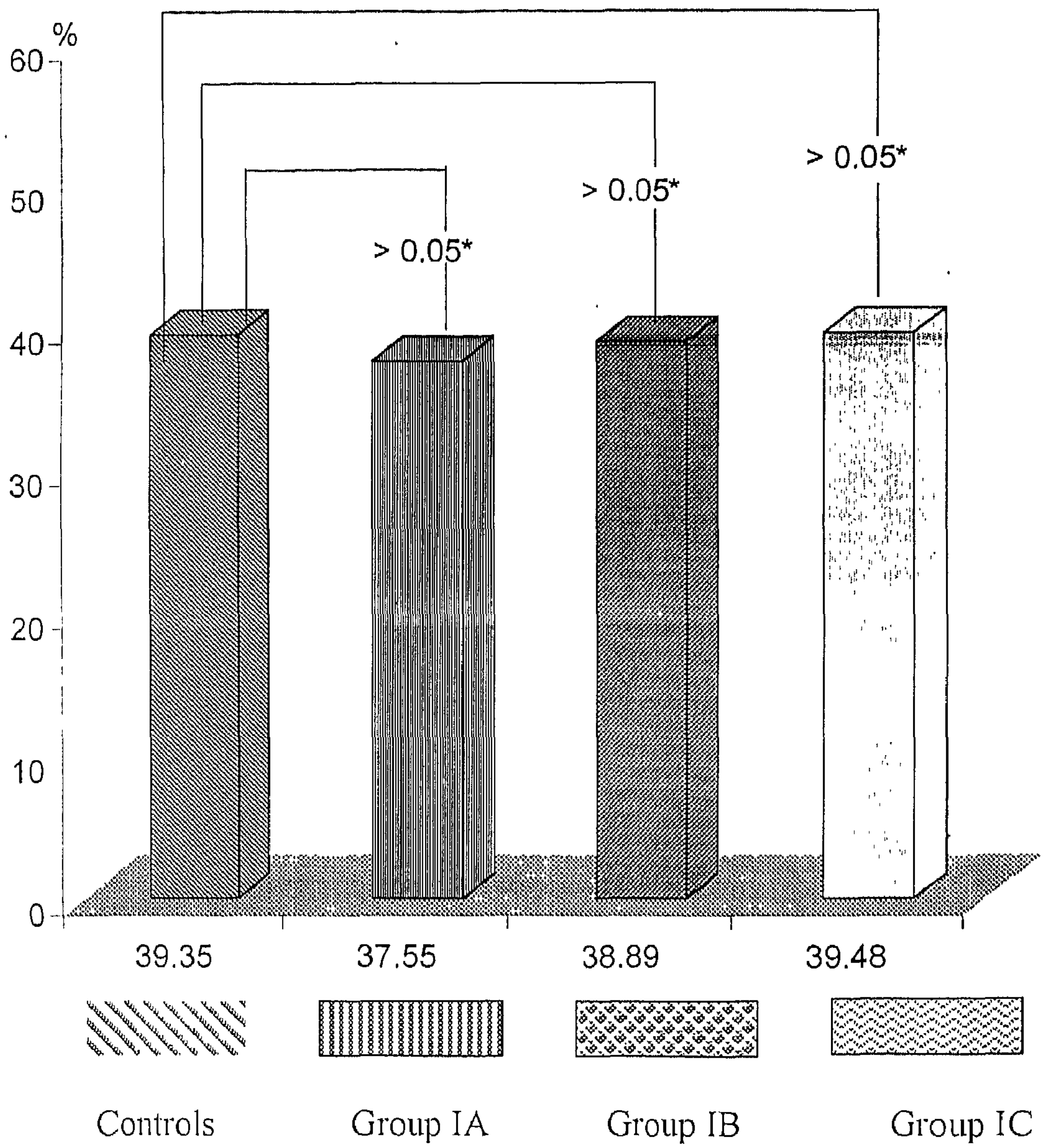
Table (14) and figures (22 & 23 & 24): show statistical comparison of rheological parameters between type-1 diabetics of a disease duration more than 10 years (group IC) and control group.

The mean value of plasma viscosity was significantly high in patients compared to controls, being 1.89 ± 0.23 in patients and 1.138 ± 0.09 in controls. ($P < 0.001$), table (14) and figure (22). On the other hand, the mean value of RBCs deformability was significantly low in patients compared to controls, being 1.35 ± 0.11 in patients and 2.32 ± 0.46 in controls. ($P < 0.001$), table (14) and figure (23). But, the mean serum fibrinogen was significantly high in patients compared to controls, being 4.16 ± 1.08 mg / dL in diabetics and 2.07 ± 0.27 gm/dL in controls. ($P < 0.001$), table (14) and figure (24).

Table (15) and figures (25 & 26 & 27): show statistical comparison of the mean value of mean flow velocities of middle

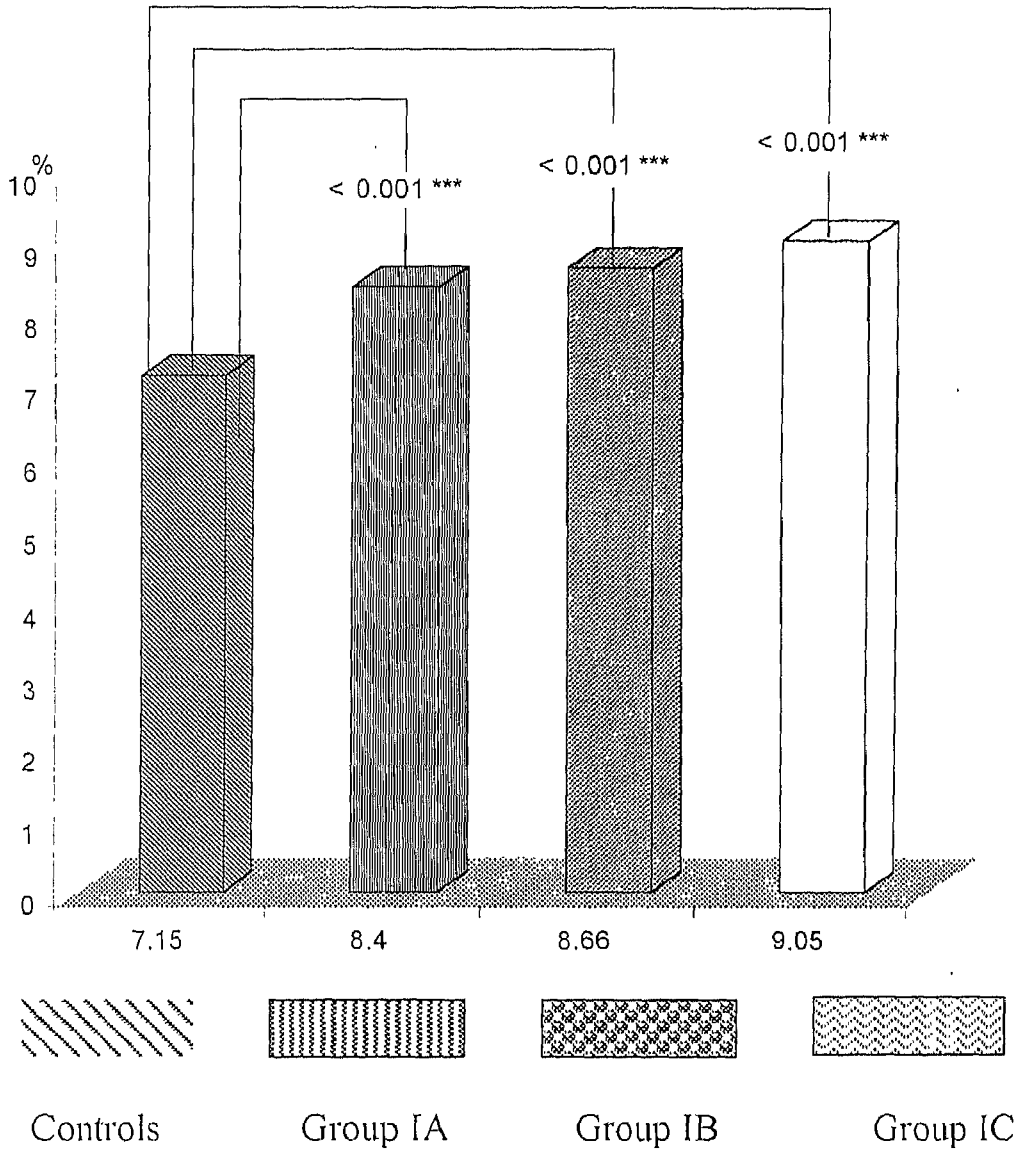
cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) and 15 minutes after its injection and mean of vasoreactivities% between type-1 diabetics of a disease duration more than 10 years and control group.

The mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (at rest) was significantly low in patients compared to controls, being 64.46 ± 10.51 cm/sec in patients and 76.46 ± 3.04 cm/sec in controls. ($P < 0.001$), table (15) and figure (25). Also, the mean value of mean flow velocities of middle cerebral arteries, (MFVs of MCAs) 15 minutes after Diamox injection was significantly low in patients compared to controls, being 73.30 ± 12.07 cm/sec in diabetics and 103.07 ± 3.52 cm / sec in controls. ($P < 0.001$) table (15) and figure (26). At the same time, the mean value of mean of vasoreactivities% was significantly low in patients compared to controls, being 13.94 ± 8.84 in patients and 34.58 ± 5.42 in controls. ($P < 0.001$), table (15) and figure (27).



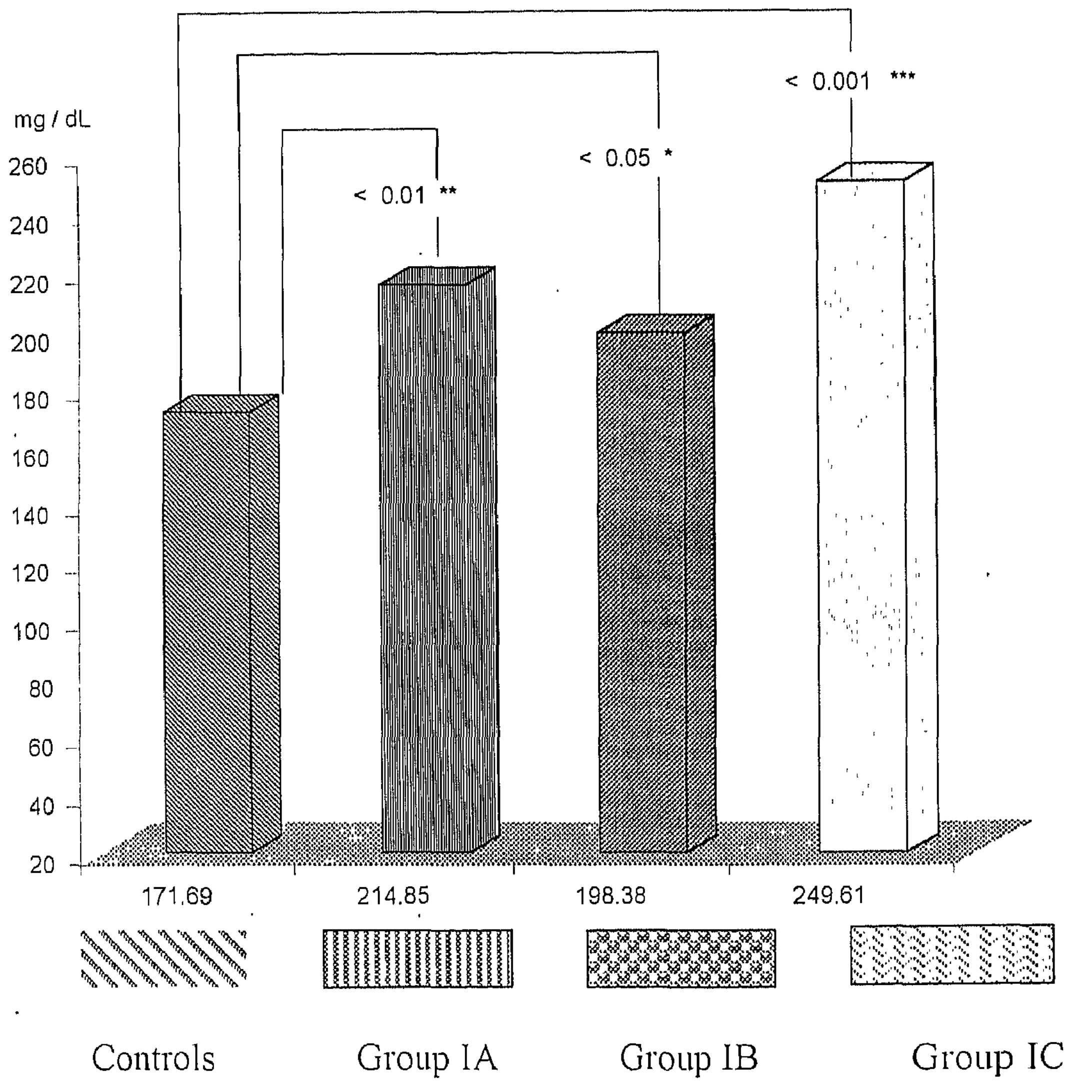
* = Non significant

Figure (16): Comparison of the mean values of hematocrit% (Hct %) in different patients' groups and controls.



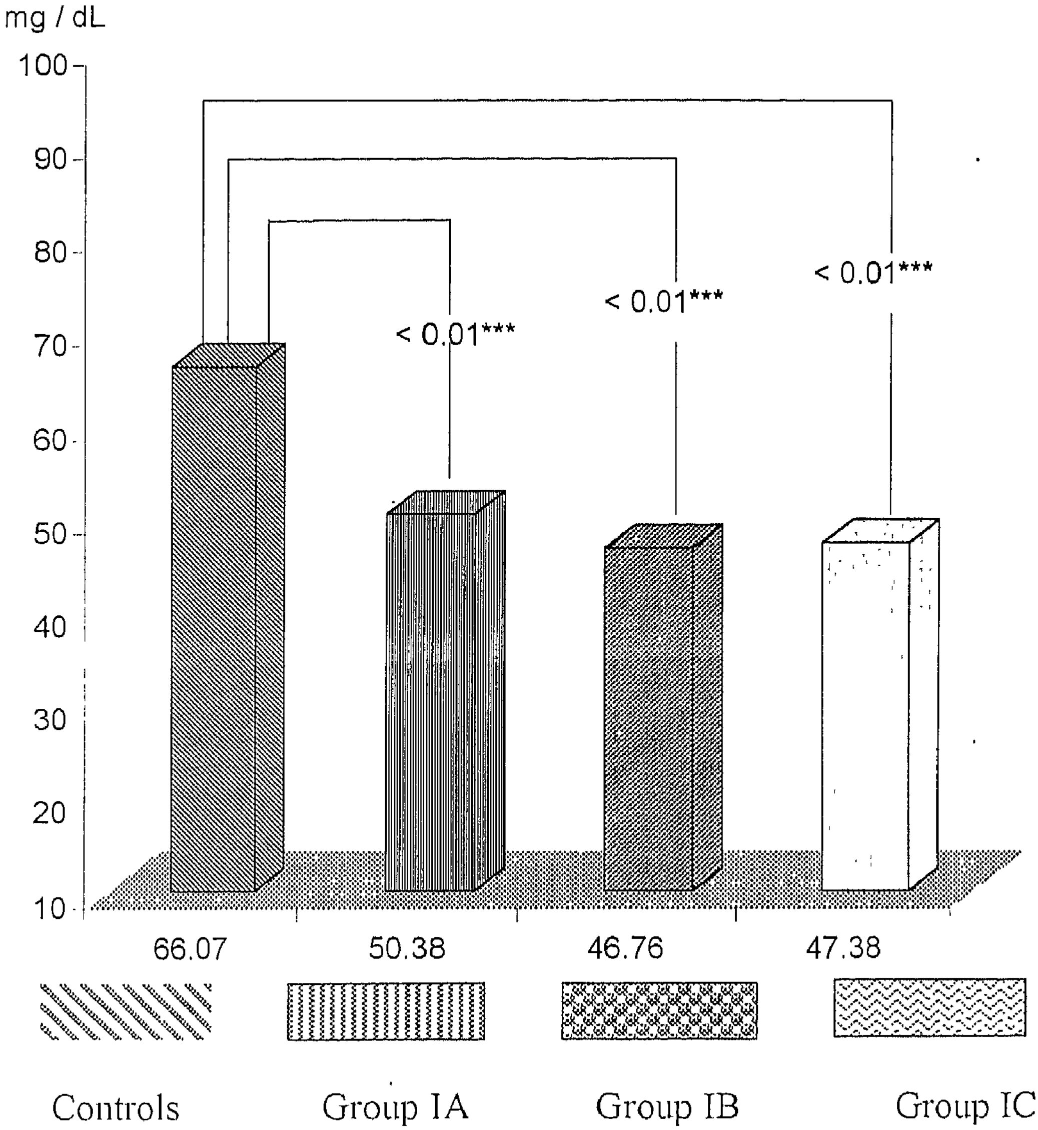
*** = Highly significant

Figure (17): Comparison of the mean values of glycated hemoglobin % (HbA1c%) in different patients' groups and controls.



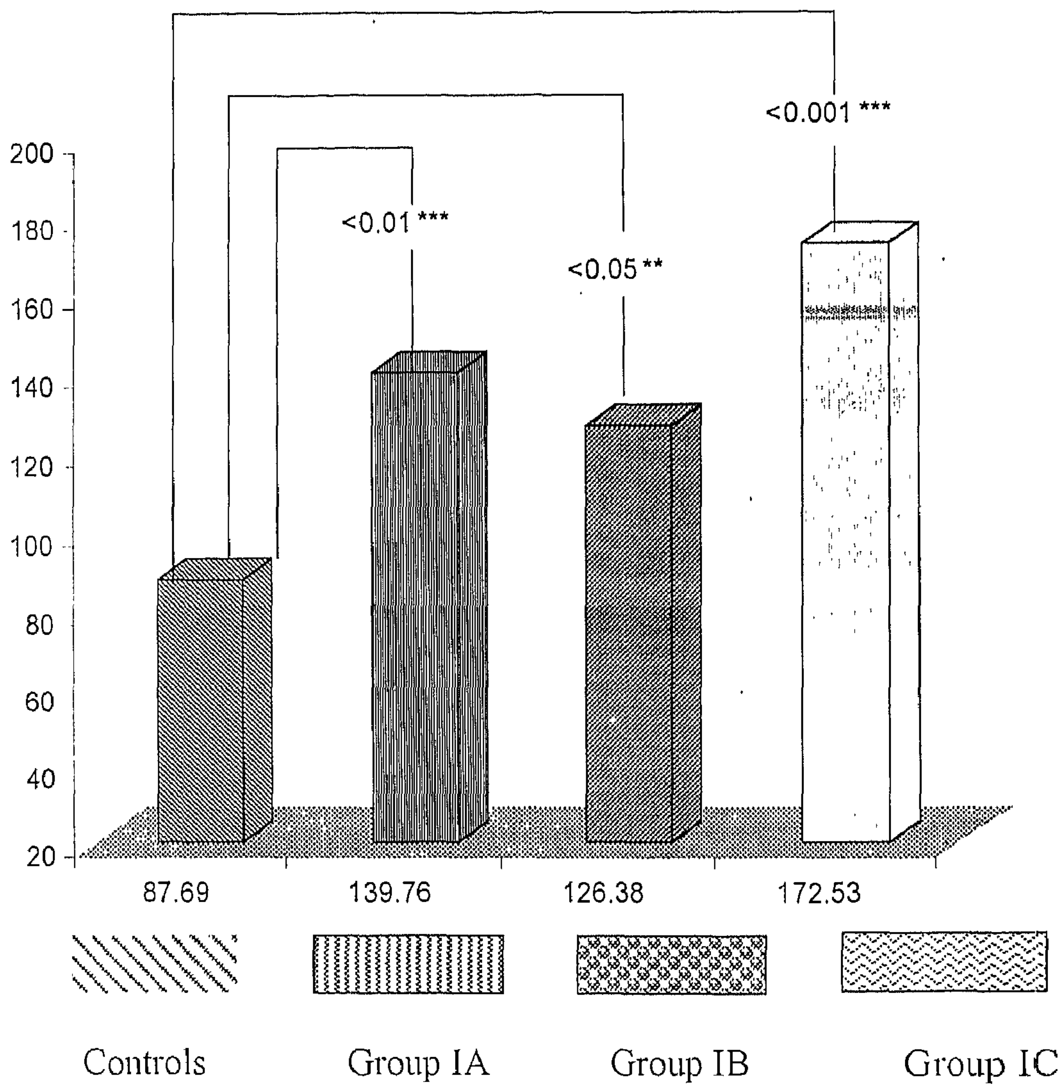
* = Non significant
*** = Highly significant

Figure (18): Comparison of the mean values of TC in different patients' groups and controls.



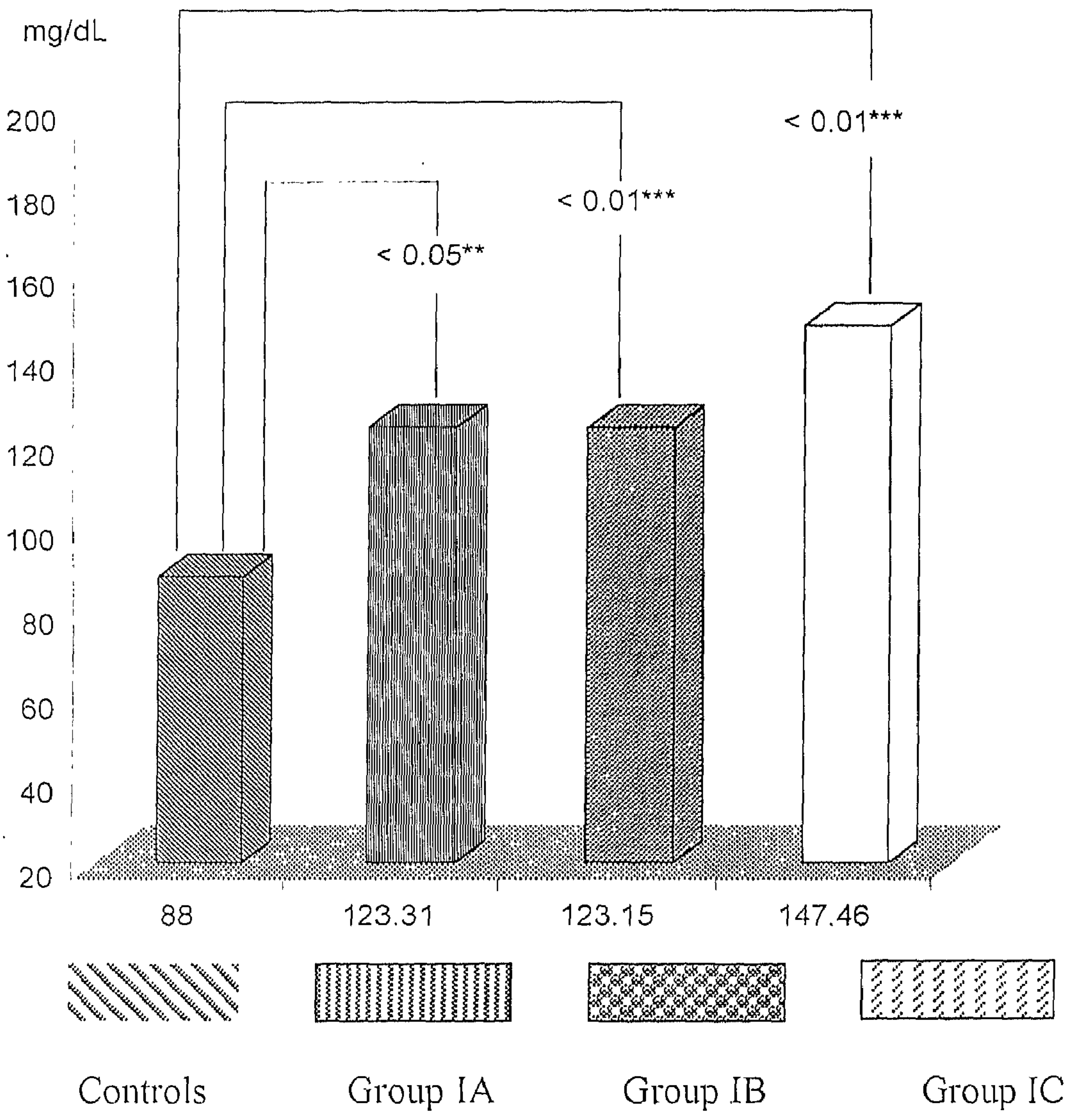
*** = Highly significant

Figure (19): Comparison of the mean values of HDL-C in different patients' groups and controls.



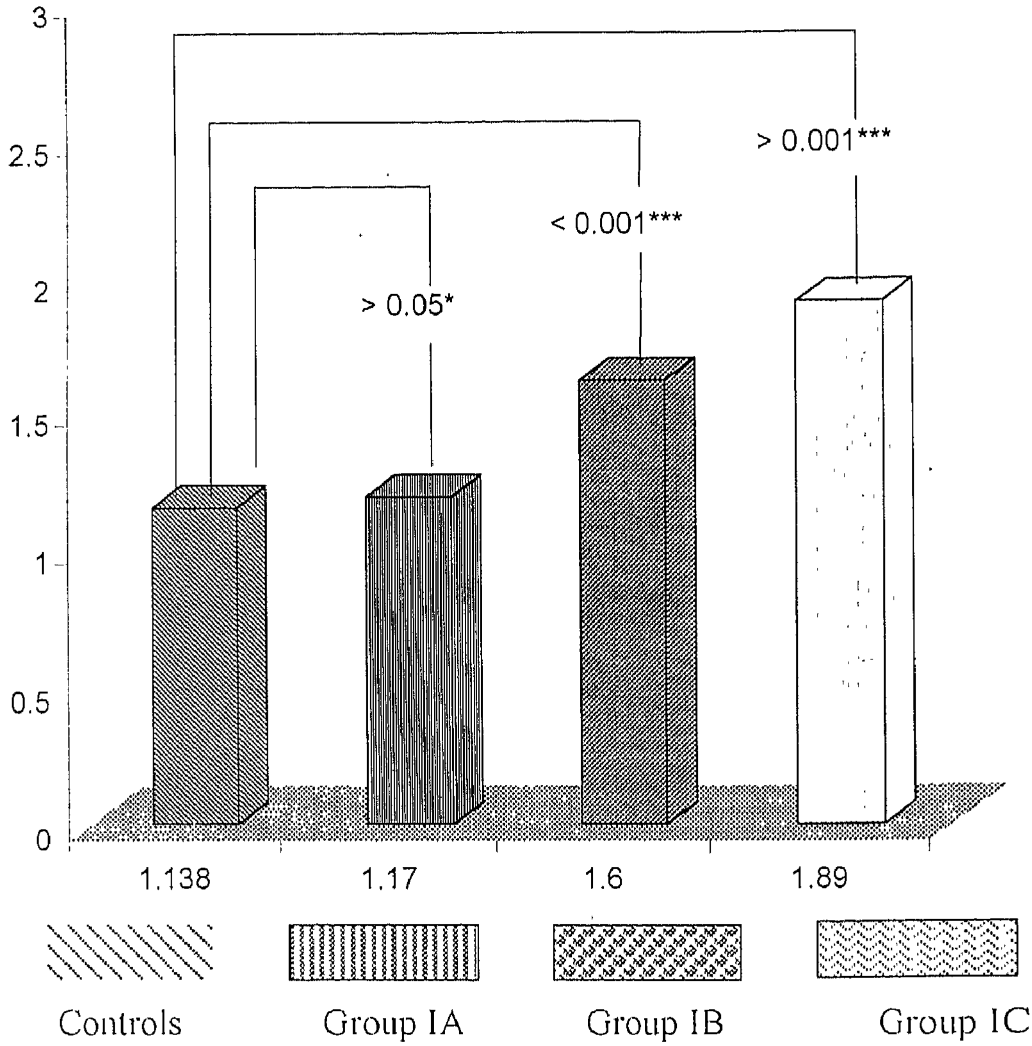
** = Significant
*** = Highly significant

Figure (20): Comparison of the mean values of LDL-C in different patients' groups and controls.



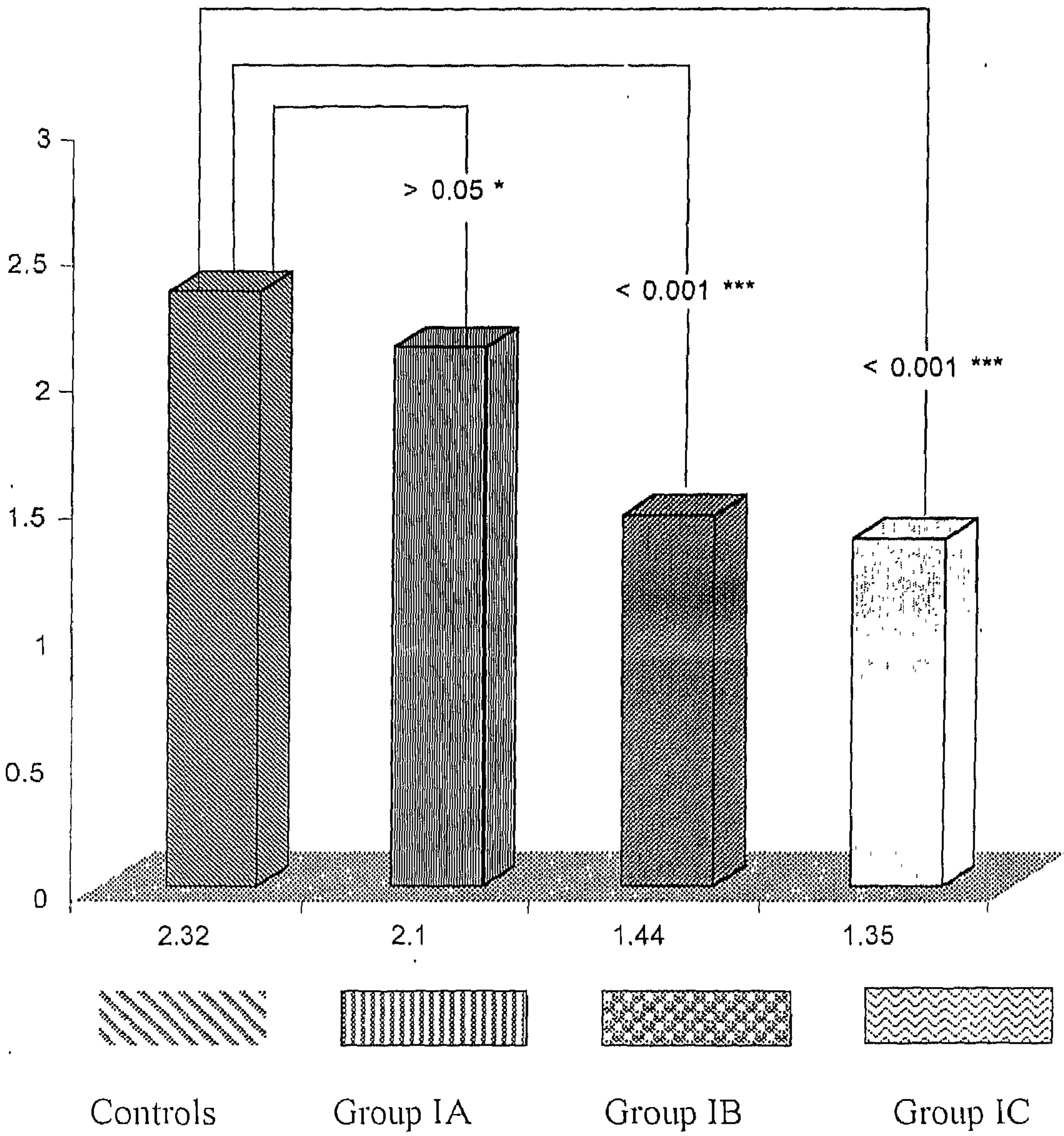
** = Significant
*** = Highly significant

Figure (21): Comparison of the mean values of TG in different patients' groups and controls.



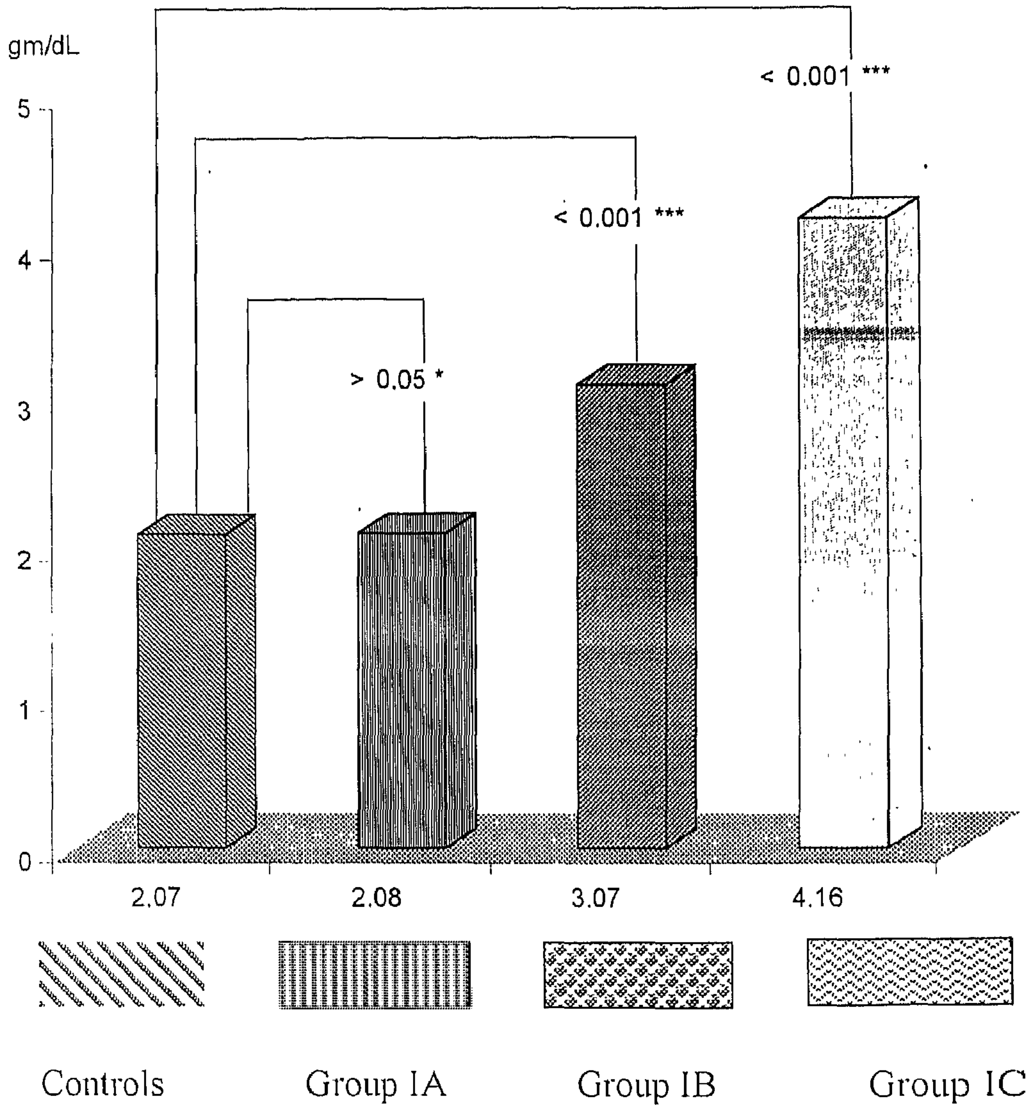
* = Non-significant
*** = Highly significant

Figure (22): Comparison of the mean values of plasma viscosity in different patients' groups and controls.



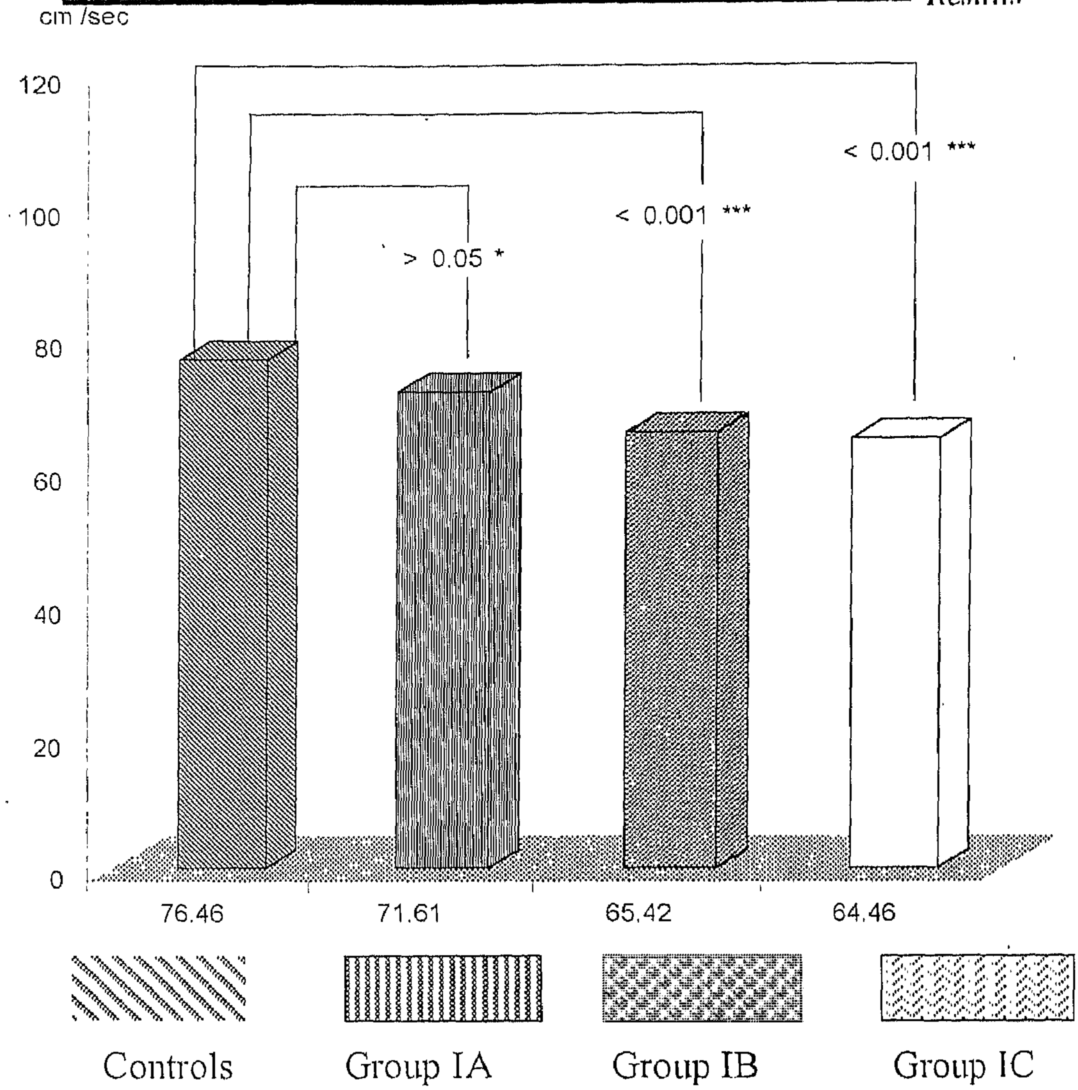
* = Non significant
*** = Highly significant

Figure (23): Comparison of the mean values of RBCs deformability in different patients' groups and controls.



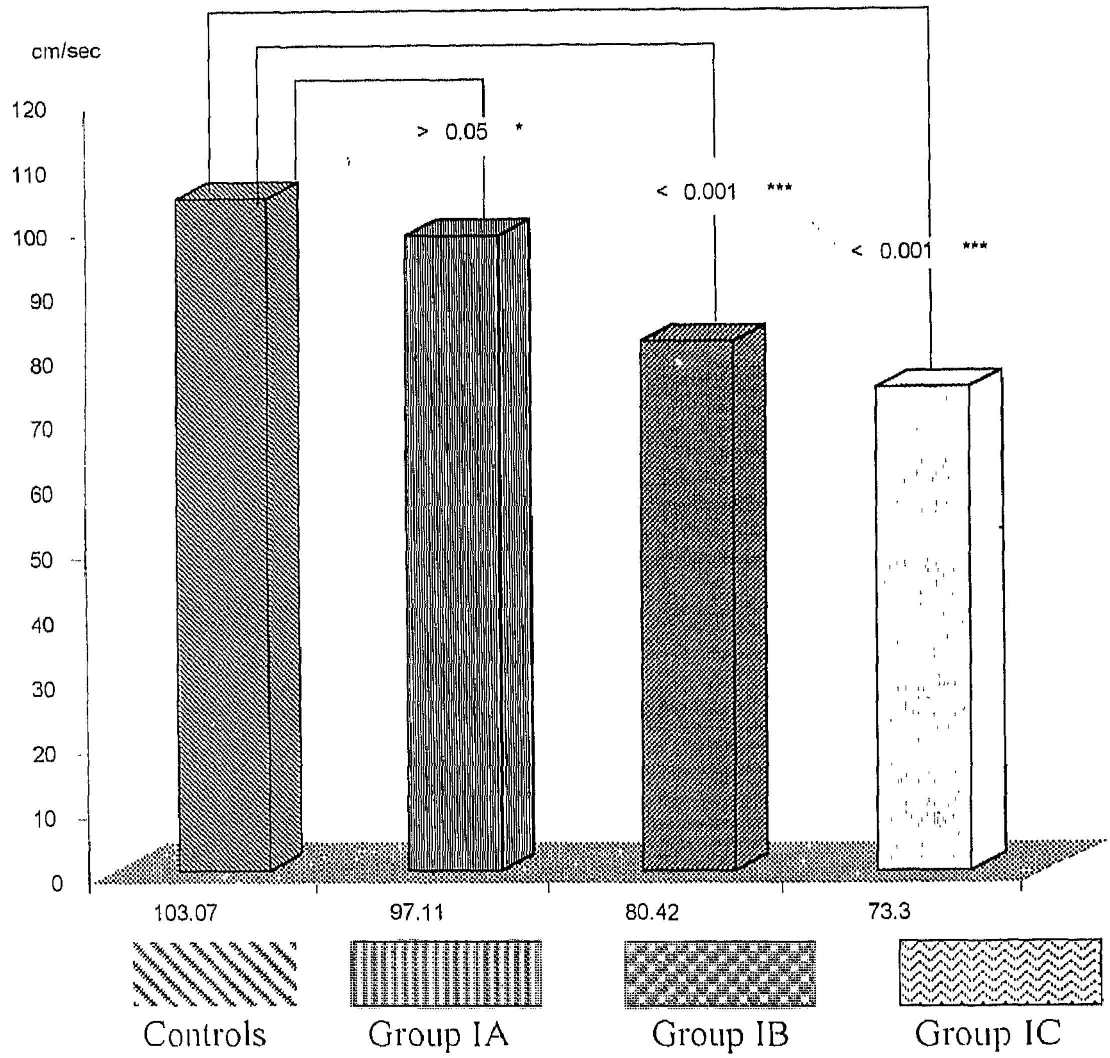
* = Non significant
*** = Highly significant

Figure (24): Comparison of the mean values of Fibrinogen in different patients' groups and controls.



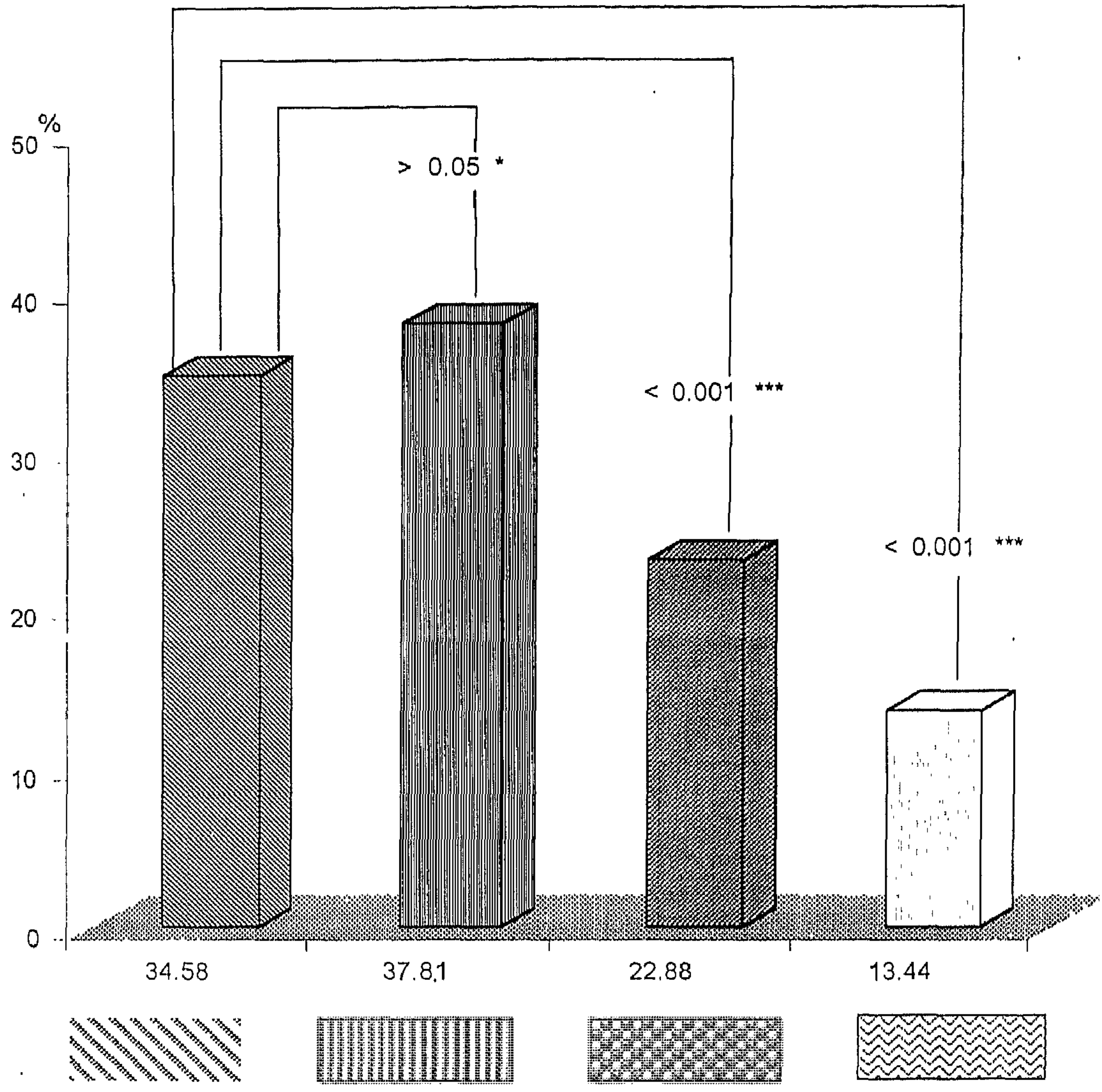
* = Non significant
*** = Highly significant

Figure (25): Comparison of the mean values of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) in different patients' groups and controls.



* = Non significant
*** = Highly significant

Figure (26): Comparison of the mean values of mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection in different patients' groups and controls.



* = Non significant
*** = Highly significant

Figure (27): Comparison of the mean values of mean of vasoreactivities% in different patients' groups and controls.

Table (16) : Comparative study of hematocrit % (Hct%) value and glycated hemoglobin % (HbA1c%) in group IA and group IB.

Group / Variable	Group IA n = 13 $\bar{X} \pm S.D.$	Group IB n = 13 $\bar{X} \pm S.D.$	"t" test	"p" value
Hematocrit% (Hct%)	37.55 ± 3.62	38.89 ± 2.72	1.07	> 0.05*
Glycated Hb% (HbA1c%)	8.4 ± 0.93	8.66 ± 1.04	0.68	> 0.05*

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

* = Non significant.

Table (17) : Comparative study of lipid profile in group IA and group IB.

Group / Variable	Group IA n = 13 $\bar{X}$ ± S.D.	Group IB n = 13 $\bar{X}$ ± S.D.	"t" test	"p" value
TC mg/dL	214.85± 46.85	198.38± 71.39	0.70	> 0.05*
HDL-C mg/dL	50.38 ± 8.88	46.76 ± 5.65	1.24	> 0.05*
LDL-C mg/dL	139.76 ±46.10	126.38±68.46	0.58	> 0.05*
TG mg/dL	123.31± 48.8	123.15 ±39.76	0.01	> 0.05*

n = Number.

$\bar{X}$ = Mean.

S.D. = Standard deviation.

TC = Total cholesterol

HDL-C = High density lipoprotein cholesterol

LDL-C = Low density lipoprotein cholesterol

TG = Triglycerides

* = Non significant

Table (18) : Comparative study of rheological data in group IA and group IB

Group / Variable	Group IA n = 13 $\bar{X} \pm S.D.$	Group IB n = 13 $\bar{X} \pm S.D.$	"t" test	"p" value
Plasma viscosity	1.17 ± 0.10	1.60 ± 0.12	9.92	$< 0.001^{***}$
RBCs Deformability	2.10 ± 0.17	1.44 ± 0.17	10.19	$< 0.001^{***}$
Fibrinogen gm /dL	2.08 ± 0.42	3.07 ± 0.63	4.69	$< 0.001^{***}$

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

*** = Highly significant

RBCs = Red blood cells.

Table (19) : Comparative study of MFVs of MCAs before and 15 minutes after Diamox injection and mean of vasoreactivities % in group IA and group IB.

Group / Variable	Group IA n = 13 $\bar{X} \pm S.D.$	Group IB n = 13 $\bar{X} \pm S.D.$	"t" test	"p" value
MFVs of MCAs before Diamox injeciton cm/sec	71.61±11.31	65.42±9.98	1.48	> 0.05*
MFVs of MCAs after Diamox injection cm/sec	97.11±14.53	80.42±12.90	3.102	< 0.01***
Mean of vaso-reactivities %	37.81 ± 5.33	22.88 ± 5.09	7.30	< 0.001***

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

MFVs = Mean flow velocities

MCAs = Middle cerebral arteries

* = Non significant

*** = Highly significant

Table (16) and figures (28 & 29) show statistical comparison of Hematocrit% (Hct%) and glycated hemoglobin% (HbA1c%) between type-1 diabetics of a disease duration less than 5 years (group IA) and those of a disease duration ranging between 5 and 10 years (group IB).

It is clearly evident that, the mean value of hematocrit% (Hct%) showed no statistically significant difference in group IA compared to its mean value in group IB, being 37.55 ± 3.62 in group IA and 38.89 ± 2.72 in group IB. (P > 0.05), table (16), and figure (28). Also, the mean value of glycated hemolgobin% (HbA1c%) showed no statistically significant difference in group IA compared to its mean value in group IB, being 8.4 ± 0.93 in group IA and 8.66 ± 1.04 in group IB. (P > 0.05), table (16) and figure (29).

Table (17) and figures (30 & 31 & 32): show statistical comparison of lipid profile between type-1 diabetics of a disease duration less than 5 years (group IA) and those of a disease duration ranging between 5 and 10 years (group IB).

The mean serum TC showed no statistically significant difference in group IA compared to its mean value in group IB, being 214.85 ± 46.85 mg /dL in group IA and 198.38 ± 71.39

mg/dL in group IB. (P > 0.05), table (17) and figure (30). Also, the mean serum HDL-C showed no statistically significant difference in group IA compared to its mean value in group IB, being 50.38 ± 8.88 mg/dL in group IA and 46.76 ± 5.65 mg / dL in group IB. (P > 0.05), table (17) and figure (31). At the same time, the mean serum LDL-C showed no statistically significant difference in group IA compared to its mean value in group IB, being 139.76 ± 46.10 mg/dL in group IA and 126.38 ± 68.46 mg/dL in group IB. (P > 0.05), table (17) and figure (32). Meanwhile, the mean serum TG showed no statistically significant difference in group IA compared to its mean value in group IB, being 123.30 ± 48.8 mg/dL in group IA and 123.15 ± 39.76 mg / dL in group IB. (P > 0.05), table (17) and figure (33).

Table (18) and figures (34 & 35 & 36): show statistical comparison of rheological parameters between type-1 diabetics of a disease duration less than 5 years (group IA) and those of a disease duration ranging between 5 and 10 years (group IB).

The mean value of plasma viscosity was significantly high in group IB compared to its mean value in group IA being, 1.60 ± 0.12 in group IB and 1.17 ± 0.10 in group IA. (P < 0.001), table (18) and figure (34). On the other hand, the mean value of RBCs deformability was significantly low in group IB compared to

its mean value in group IA being 1.44 ± 0.17 in group IB and 2.10± 0.17 in group IA. (P < 0.001),.table (18) and figure (35). But, the mean serum fibrinogen was significantly high in group IB compared to its mean value in group IA, being 3.07 ± 0.63 gm /dL in group IB and 2.08 ± 0.42 gm / dL in group IA. (P < 0.001) table (18) and figure (36).

Table (19) and figures (37 & 38 & 39): show statistical comparison of the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) and 15 minutes after its injection and mean of vasoreactivities% between type-1 diabetics of a disease duration less than 5 years (group IA) and those of a disease duration ranging between 5 and 10 years (group IB).

The mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) showed no statistically significant difference in group IA compared to its mean value in group IB, being, 71.61 ± 11.31 cm /sec in group IA and 65.42 cm/sec in group IB. (P > 0.05), table (19) and figure (37). But, the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection was significantly low in group IB compared to its mean value in group IA being 80.42 ± 12.90 cm/sec in group IB and

97.11 ± 14.53 cm/sec in group IA.(P $\leq$ 0.01), table (19) and figure (38). Also, the mean value of mean of vasoreactivities % was significantly low in group IB compared to its mean value in group IA, being 22.88 ± 5.09 in group IB and 37.81 ± 5.33 in group IA. (P < 0.001), table (19) and figure (39).

Table (20) : Comparative study of hemotoerit % (Hct%) value and glycated hemoglobin % (HbA1c%) in group IA and group IC.

Group / Variable	Group IA n = 13 $\bar{X} \pm$ S.D.	Group IC n = 13 $\bar{X} \pm$ S.D.	"t" test	"p" value
Hematocrit% (Hct%)	37.55 ± 3.62	39.48 ± 2.71	1.54	> 0.05*
Glycated Hb% (HbA1c%)	8.4 ± 0.93	9.05 ± 0.58	2.14	< 0.05**

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

* = Non significant

** = Significant.

Table (21) : Comparative study of lipid profile in group IA and group IC

Group / Variable	Group IA n = 13 $\bar{X} \pm$ S.D.	Group IC n = 13 $\bar{X} \pm$ S.D.	"t" test	"p" value
TC mg/dL	214.85± 46.85	249.61±59.22	1.66	> 0.05*
HDL-C mg/dL	50.38±8.88	47.38±3.04	1.15	> 0.05*
LDL-C mg/dL	139.76±46.10	172.53±54.96	1.65	> 0.05*
TG mg/dL	123.31± 48.8	147.46 ±59.87	1.13	> 0.05*

n = Number.

$\bar{X}$ = Mean.

S.D. = Standard deviation.

TC = Total cholesterol

HDL-C = High density lipoprotein cholesterol

LDL-C = Low density lipoprotein cholesterol

TG = Triglycerides

* = Non significant

Table (22) : Comparative study of rheological data in group IA and group IC

Group / Variable	Group IA n = 13 $\bar{X} \pm$ S.D.	Group IC n = 13 $\bar{X} \pm$ S.D.	"t" test	"p" value
Plasma viscosity	1.17 ± 0.10	1.89 ± 0.23	10.58	< 0.001***
RBCs Deformability	2.10 ± 0.17	1.35 ± 0.11	10.36	< 0.001***
Fibrinogen gm /dL	2.08 ± 0.42	4.16 ± 1.08	6.46	< 0.001***

n = Number

$\bar{X}$ = Mean

S.D. Standard deviation

*** = Highly significant

RBCs = Red blood cells.

Table (23) : Comparative study of MFVs of MCAs before and 15 minutes after Diamox injection and mean of vasoreactivities % in group IA and group IC.

Group / Variable	Group IA n = 13 $\bar{X} \pm$ S.D.	Group IC n = 13 $\bar{X} \pm$ S.D.	"t" test	"p" value
MFVs of MCAs before Diamox injeciton cm/sec	71.61±11.31	64.46±10.51	1.67	> 0.05*
MFVs of MCAs after Diamox injection cm/sec	97.11±14.53	73.30±12.07	4.54	< 0.001***
Mean of vaso-reactivities %	37.81 ± 5.33	13.44 ± 8.84	8.52	< 0.001***

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

MFVs = Mean flow velocities

MCAs = Middle cerebral arteries

* = Non significant

*** = Highly significant

Table (20) and figures (28 & 29): show statistical comparison of hematocrit% (Hct%) and glycated hemoglobin % (HbA1c%) between type-1 diabetics of a disease duration less than 5 years (group IA) and those of a disease duration more than 10 years (group IC).

It is clearly evident that, the mean value of hematocrit % (Hct %) showed no statistically significant difference in group IA compared to its mean value in group IC, being, 37.55±3.62 in group IA and 39.48 ± 2.71 in group IC. (P > 0.05), table (20) and figure (28). But, the mean value of glycated hemoglobin % (HbA1c%) was low in group IA compared to its mean value in group IC, being 8.4 ± 0.93 in group IA and 9.05 ± 0.58 in group IC. (P< 0.01), table (20) and figure (29).

Table (21) and figures (30 & 31 & 32 & 33): show statistical comparison of lipid profile between type-1 diabetics of a disease duration less than 5 years (group IA) and those of a disease duration more than 10 years (group IC).

The mean serum TC showed no statistically significant difference in group IA compared to its mean value in group IC, being 214.85 ± 46.85 mg / dL in group IA and 249.61 ± 59.22 in group IC. (P > 0.05), table (21) and figure (30). Also, the mean

serum HDL-C showed no statistically significant difference in group IA compared to its mean value in group IC. Being 50.38 ± 8.88 mg/dL in group IA and 47.38 ± 3.04 mg /dL in group IC. (P > 0.05) table (21) and figure (31). At the same time, the mean serum LDL-C showed no statistically significant difference in group IA compared to its mean value in group IC, being 139.76 ± 46.10 mg / dL in group IA and 172.53 ± 54.96 mg/dL in group IC. (P > 0.05), table (21) and figure (32).

Meanwhile, the mean serum TG showed no statistically significant difference in group IA compared to its mean value in group IC, being 123.31 ± 48.8 mg /dL in group IA and 147.46 ± 59.87 mg/dL in group IC. (P > 0.05), table (21) and figure (33).

Table (22) and figures (34 & 35 & 36): show statistical comparison of rheological parameters between type-1 diabetics of a disease duration less than 5 years (group IA) and those of a disease duration more than 10 years (group IC).

The mean value of plasma viscosity was significantly high in group IC compared to its mean value in group IA, being 1.89 ± 0.23 in group IC and 1.17 ± 0.10 in group IA. (P < 0.001), table (22) and figure (34). On the other hand, the mean value of RBCs deformability was significantly low in group IC compared to its mean value in group IA being 1.35 ± 0.11 in group IC and

2.10 ± 0.17 in group IA. (P < 0.01) table (22) and figure (35). But, the mean serum fibrinogen was significantly high in group IC compared to its mean value in group IA, being 4.16 ± 1.08 gm /dL in group IC and 2.08 ± 0.42 gm / dL in group IA. (P < 0.001), table (22) and figure (36).

Table (23) and figures (37 & 38 & 39): show statistical comparison of the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) and 15 minutes after its injection and mean of vasoreactivities% between type-1 diabetics of a disease duration less than 5 years (group IA) and those of a disease duration more than 10 years (group IC).

The mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) showed no statistically significant difference in group IC compared to its mean value in group IA, being 64.46 ± 10.51 cm/sec in group IC and 71.61 ± 11.31 cm / sec in group IA. (P > 0.05), table (23) and figure (37). But the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection was significantly low in group IC compared to its mean value in group IA, being 73.30 ± 12.07 cm / sec in group IC and 97.11 ± 14.53 cm / sec in group IA. (P < 0.001) table (23) and

figure (38). At the same time, the mean value of mean of vasoreactivities% was significantly low in group IC compared to its mean value in group IA being 13.44 ± 8.84 in group IC and 37.81 ± 5.33 in group IA. ($P < 0.01$) table (23) and figure (39).

Table (24) : Comparative study of hematocrit % (Hct%) value and glycated hemoglobin% (HbA1c%) in group IB and group IC.

Group / Variable	Group IB n = 13 $\bar{X} \pm S.D.$	Group IC n = 13 $\bar{X} \pm S.D.$	"t" test	"p" value
Hematocrit% (Hct%)	38.89 ± 2.72	39.48 ± 2.71	0.56	>0.05*
Glycated Hb% (HbA1c%)	8.66 ± 1.04	9.05 ± 0.58	1.18	>0.05*

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

* = Non significant

Table (25) : Comparative study of lipid profile in group IB and group IC

Group / Variable	Group IB n = 13 $\bar{X} \pm$ S.D.	Group IC n = 13 $\bar{X} \pm$ S.D.	"t" test	"p" value
TC mg/dL	198.38 ± 71.39	249.61±59.22	1.99	< 0.05**
HDL-C mg/dL	46.76±5.65	47.38 ± 3.04	0.35	> 0.05*
LDL-C mg/dL	126.38± 68.46	172.53±54.96	1.90	< 0.05**
TG mg/dL	123.15±39.46	147.46±59.87	1.22	> 0.05*

n = Number.

$\bar{X}$ = Mean.

S.D. = Standard deviation.

TC = Total cholesterol

HDL-C = High density lipoprotein cholesterol

LDL-C = Low density lipoprotein cholesterol

TG = Triglycerides

* = Non significant

** = Significant

Table (26) : Comparative study of rheological data in group IB and group IC

Group / Variable	Group IB n = 13 $\bar{X} \pm S.D.$	Group IC n = 13 $\bar{X} \pm S.D.$	"t" test	"p" value
Plasma viscosity	1.60 ±0.12	1.89 ± 0.23	4.03	< 0.001***
RBCs Deformability	1.44 ± 0.17	1.35 ± 0.11	1.66	> 0.05*
Fibrinogen gm /dL	3.07 ± 0.63	4.16 ± 1.08	3.15	< 0.01***

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

RBCs = Red blood cells.

* = Non significant

*** = Highly significant

Table (27) : Comparative study of MFVs of MCAs before and 15 minutes after Diamox injection and mean of vasoreactivities % in group IB and group IC.

Group / Variable	Group IB n = 13 $\bar{X} \pm$ S.D.	Group IC n = 13 $\bar{X} \pm$ S.D.	"t" test	"p" value
MFVs of MCAs before Diamox injeciton cm/sec	65.42 ± 9.98	64.46 ± 10.51	0.24	> 0.05*
MFVs of MCAs after Diamox Injection cm/sec	80.42 ±12.90	73.30±12.07	1.45	> 0.05*
Mean of vaso-Reactivities %	22.88 ±5.09	13.44±8.84	3.35	< 0.01***

n = Number

$\bar{X}$ = Mean

S.D. = Standard deviation

MFVs = Mean flow velocities.

MCAs = Middle cerebral arteries

* = Non significant

*** = Highly significant.

Table (24) and figures (28 & 29): show statistical comparison of hematocrit % (Hct%) and glycated hemoglobin % (HbA1c%) between type-1 diabetics of a disease duration ranging between 5 and 10 years (group IB) and those of a disease duration more than 10 years (group IC).

The mean value of hematocrit % (Hct %) showed no statistically significant difference in group IB compared to its mean value in group IC being, 38.89 ± 2.72 in group IB and 39.48 ± 2.71 in group IC. (P > 0.05), table (24) and figure (28). Also, the mean value of glycated hemoglobin % (HbA1c%) showed no statistically significant difference in group IB compared to its mean value in group IC being, 8.66 ± 1.04 in group IB and 9.05 ± 0.58 in group IC. (P > 0.05), table (24) and figure (29).

Table (25) and figures (30 & 31 & 32 & 33) : show statistical comparison of lipid profile between type-1 diabetics of a disease duration ranging between 5 and 10 years (group IB) and those of a disease duration more than 10 years (group IC).

The mean serum TC was significantly high in group IC compared to its mean values in group IB being, 249.62 ± 59.22 mg/dL in group IC and 198.38±71.39 mg/dLin group IC. (P < 0.05), table (25) and figure (30). On the other hand, the mean

serum HDL-C showed no statistically significant difference in group IB compared to its mean value in group IC being, 46.76 ± 5.66 mg /dL in group IB and 47.38 ± 3.04 mg / dL in group IC. (P > 0.05), table (25) and figure (31).

But, the mean serum LDL-C was significantly high in group IC compared to its mean value in group IB being, 172.53 ± 54.96 mg/dL in group IC and 126.38 ± 68.46 mg/dL in group IB. (P < 0.05), table (25) and figure (32). On the other hand, the mean serum TG showed no statistically significant difference in group IB compared to its mean value in group IC being, 123.15± 39.76 mg/dL in group IB and 147.46 ± 59.87 mg / dL in group IC. (P > 0.05), table (25) and figure (33).

Table (26) and figures (34 & 35 & 36) : show statistical comparison of rheological parameters between type-1 diabetics of a disease duration ranging between 5 and 10 years (group IB) and those of a disease duration more than 10 years (group IC).

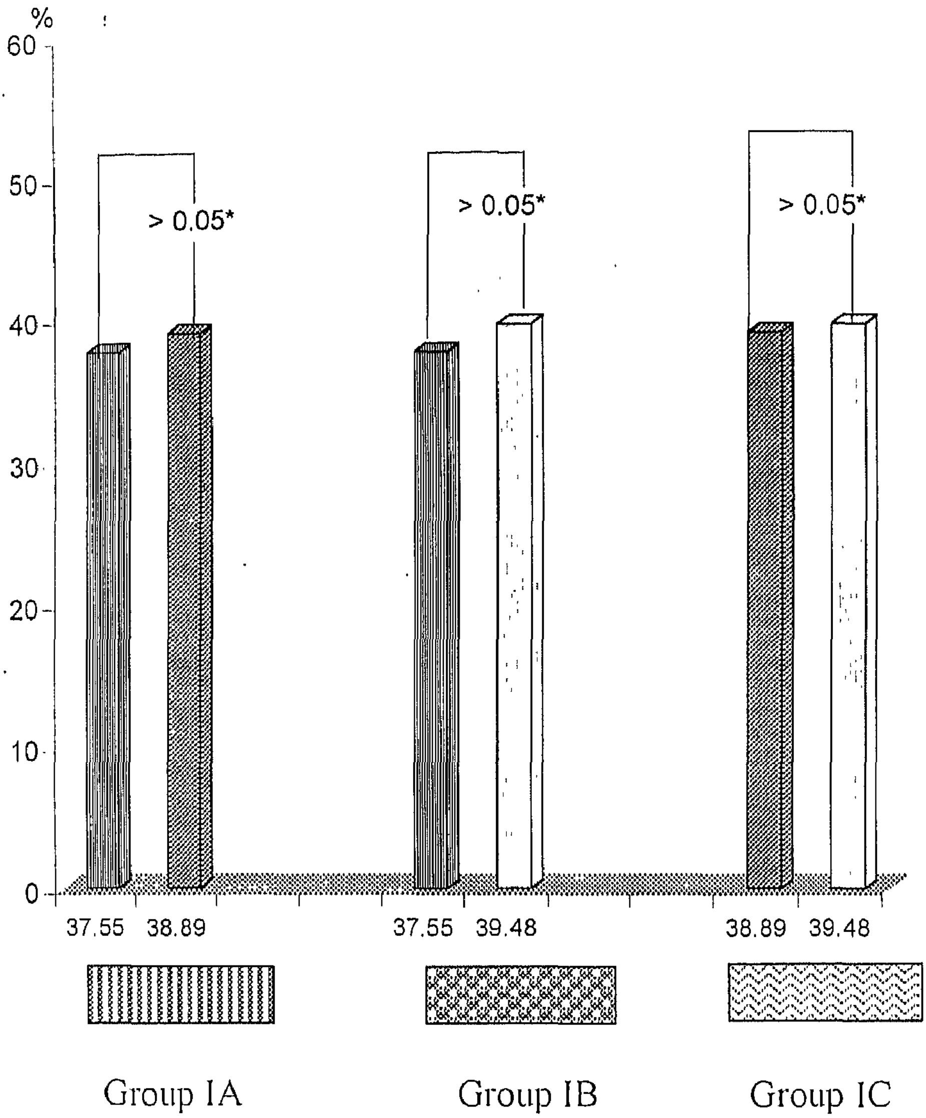
The mean value of plasma viscosity was significantly high in group IC compared to its mean value in group IB being, 1.89 ± 0.23 in group IC and 1.60 ± 0.12 in group IB. (P < 0.001), table (26) and figure (34). But, the mean value of RBCs deformabililty showed no statistically significant difference in group IB compared to its mean value in group IC being, 1.44 ± 0.17 in group IB and 1.35 ± 0.11 in

group IC. ($P > 0.05$), table (26) and figure (35). On the other hand, the mean serum fibrinogen was significantly high in group IC compared to its mean value in group IB, being 4.16 ± 1.08 gm / dL in group IC and 3.07 ± 0.63 gm / dL in group IB. ($P < 0.01$), table (26) and figure (36).

Table (27) and figures (37 & 38 & 39) : show statistical comparison of the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) and 15 minutes after its injection and mean of vasoreactivities% between type-1 diabetics of a disease duration ranging between 5 and 10 years (group IB) and those of a disease duration more than 10 years (group IC).

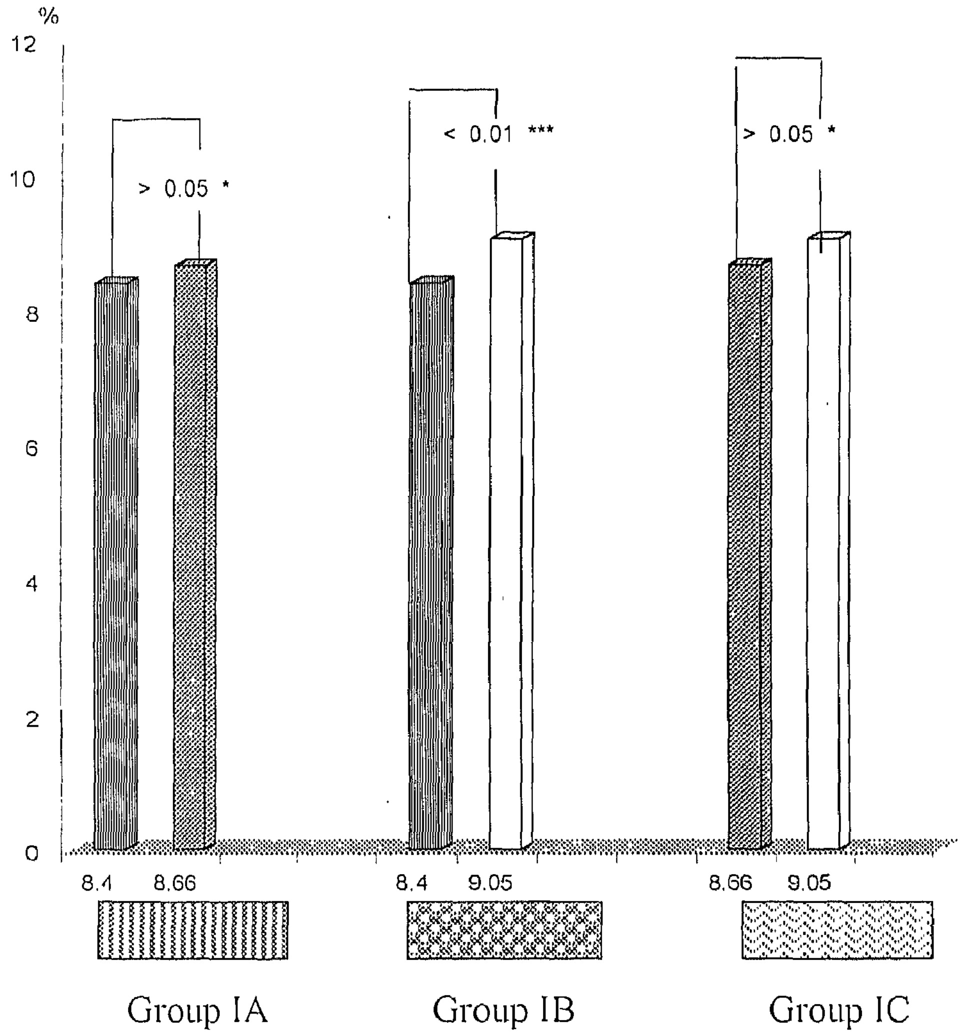
The mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) showed no statistically significant difference in group IB compared to its mean value in group IC being, 65.42 ± 9.98 cm /sec in group IB and 64.46 ± 10.51 cm / sec in group IC. ($P > 0.05$), table (27) and figure (37). Also, the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection showed no statistically significant difference in group IB compared to its mean value in group IC being, 80.42 ± 12.9 cm/sec in group IB and 73.30 ± 12.07 cm/sec in group IC. ($P > 0.05$),

table (27) and figure (38). On the other hand, the mean value of mean of vasoreactivities% was significantly low in group IC compared to its mean value in group IB being, 13.44 ± 8.84 in group IC and 22.88 ± 5.09 in group IB. ($P < 0.01$) table (27) and figure (39).



* = Non significant

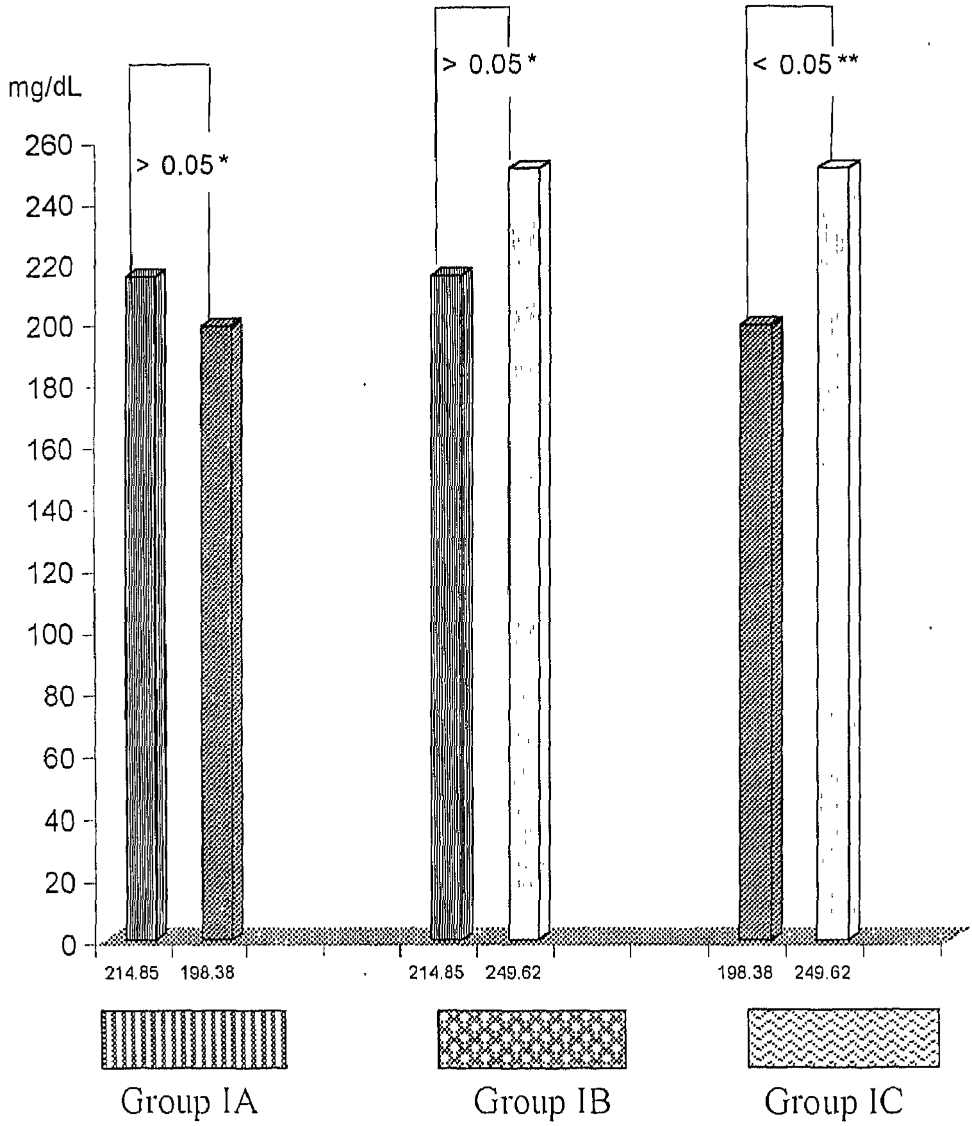
Figure (28): Comparison of the mean values of hematocrit% (Hct%) in different patients' groups.



* = Non significant

*** = Highly significant

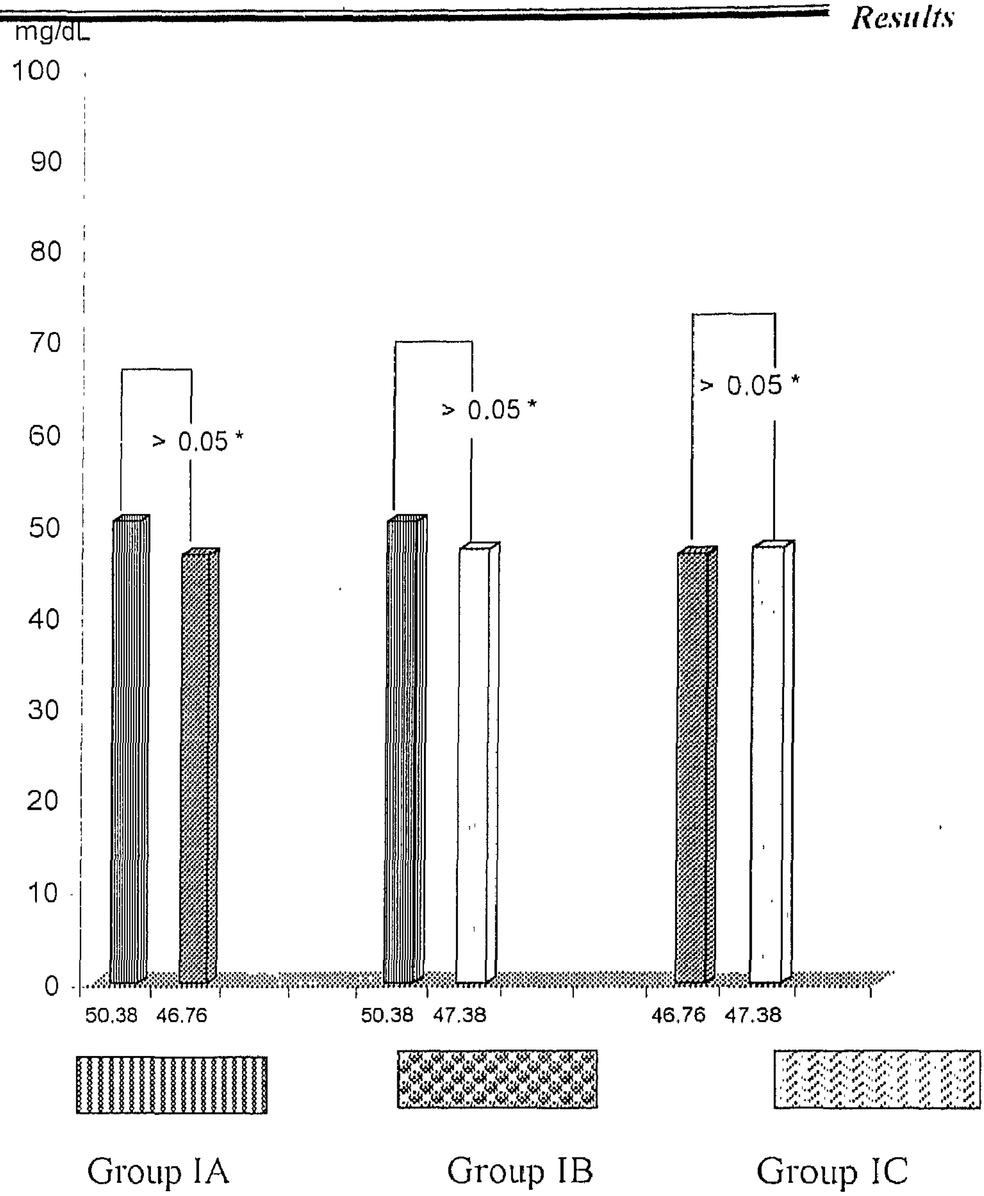
Figure (29): Comparison of the mean values of glycated hemoglobin% (HbA1c%) in different patients' groups.



* = Non significant

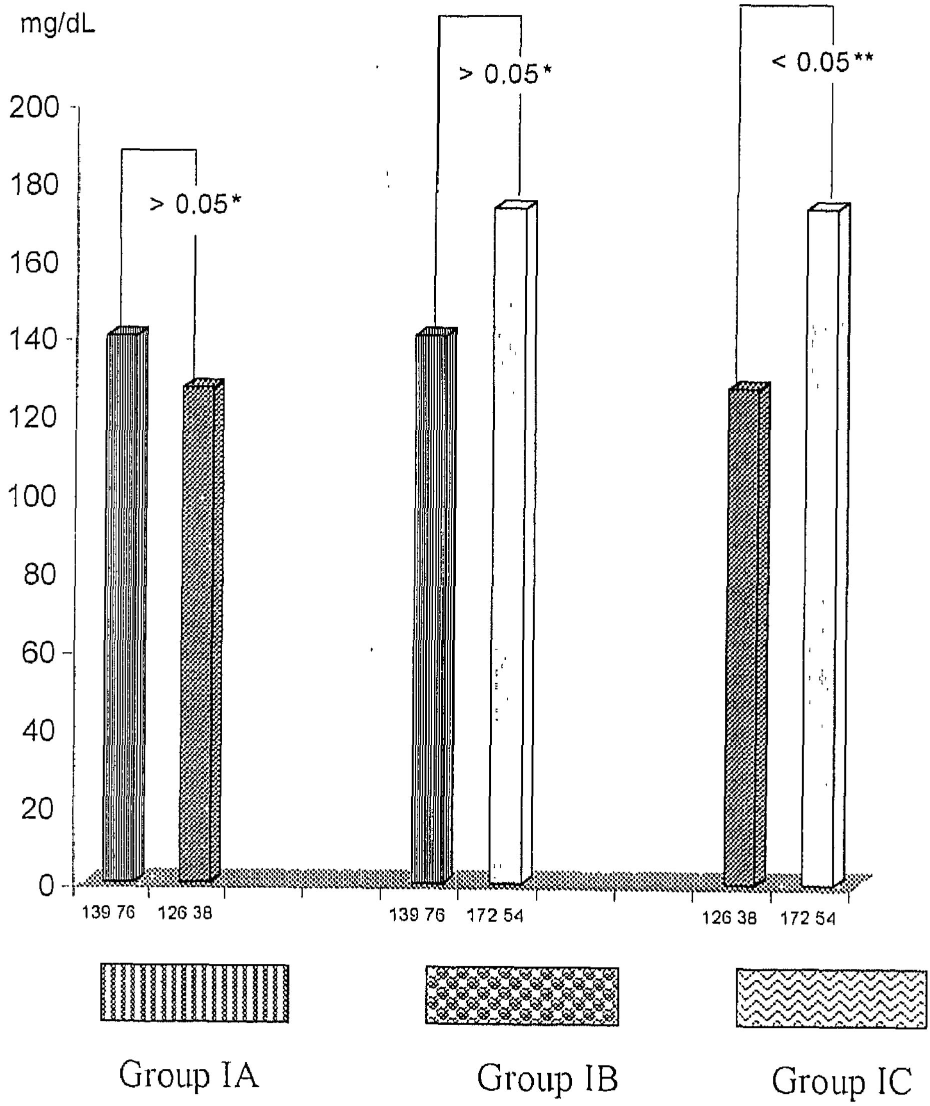
** = Significant

Figure (30): Comparison of the mean values of TC in different patients' groups.



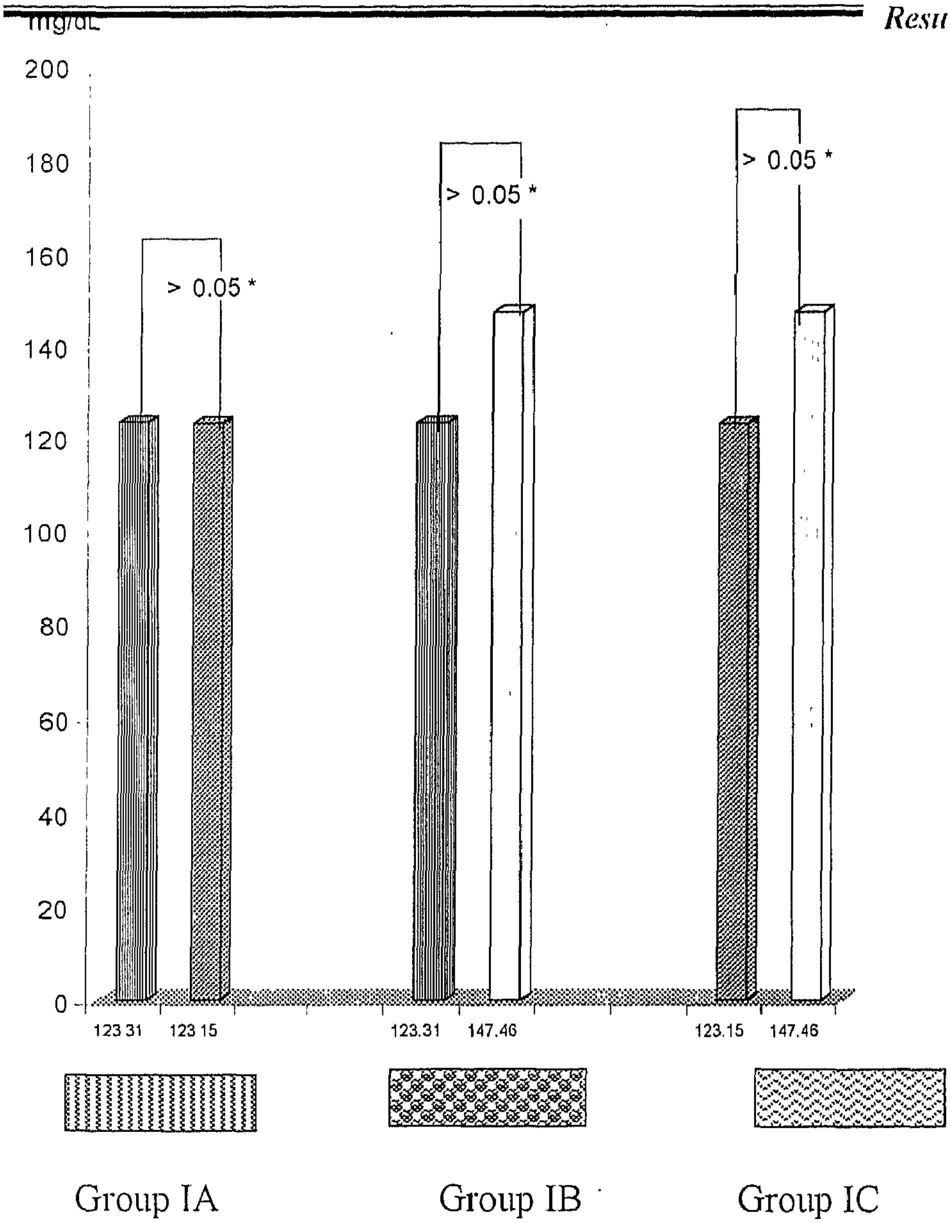
* = Non significant

Figure (31): Comparison of the mean values of HDL-C in different patients' groups.



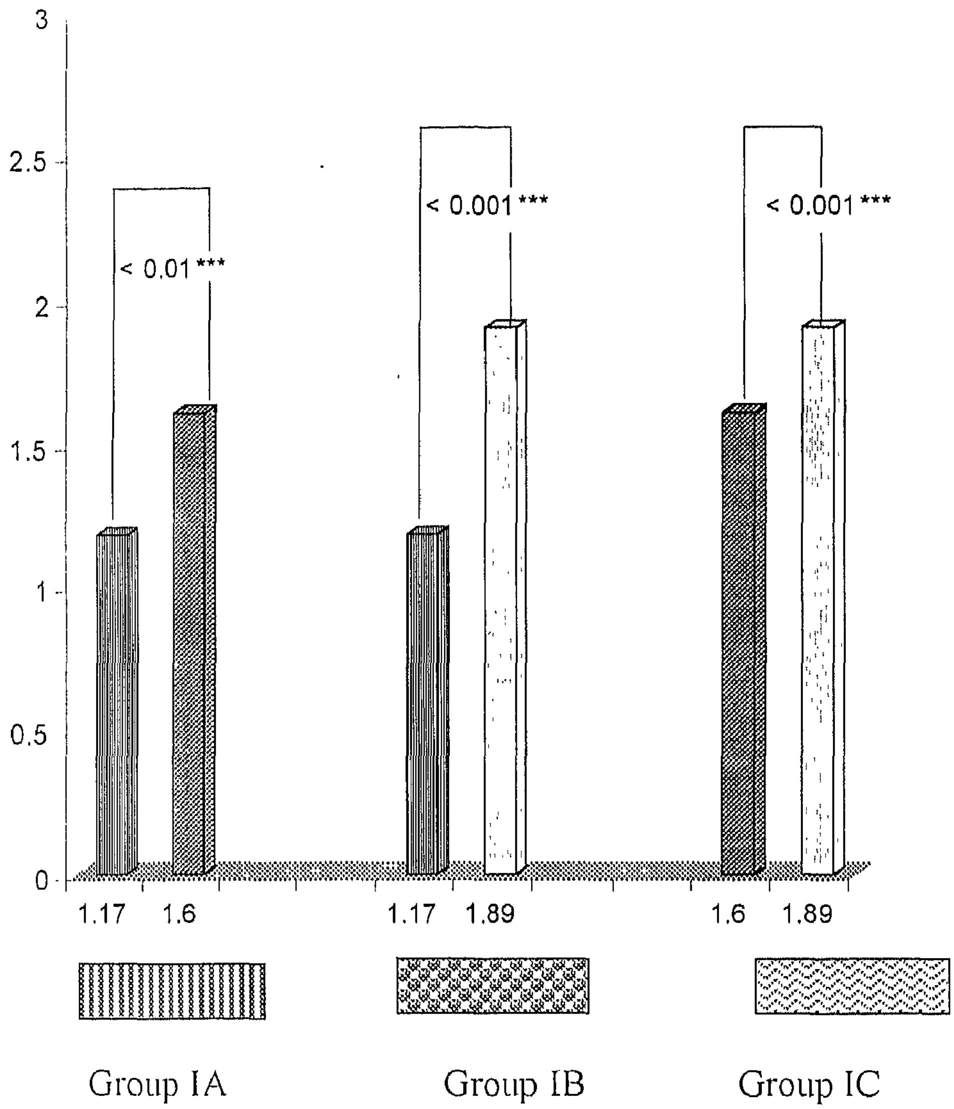
* = Non significant
** = Significant

Figure (32): Comparison of the mean values of LDL-C in different patients' groups.



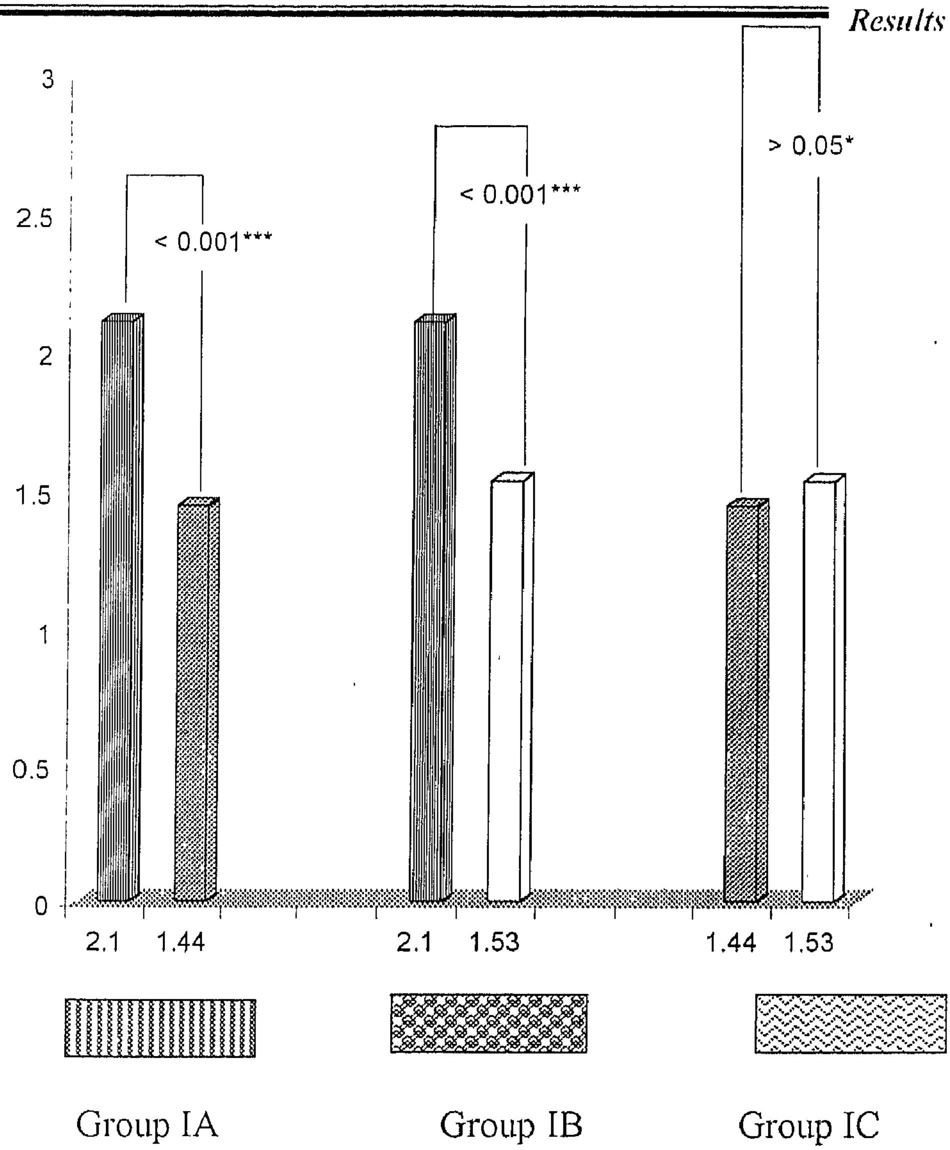
* = Non significant

Figure (33): Comparison of the mean values of TG in different patients' groups.



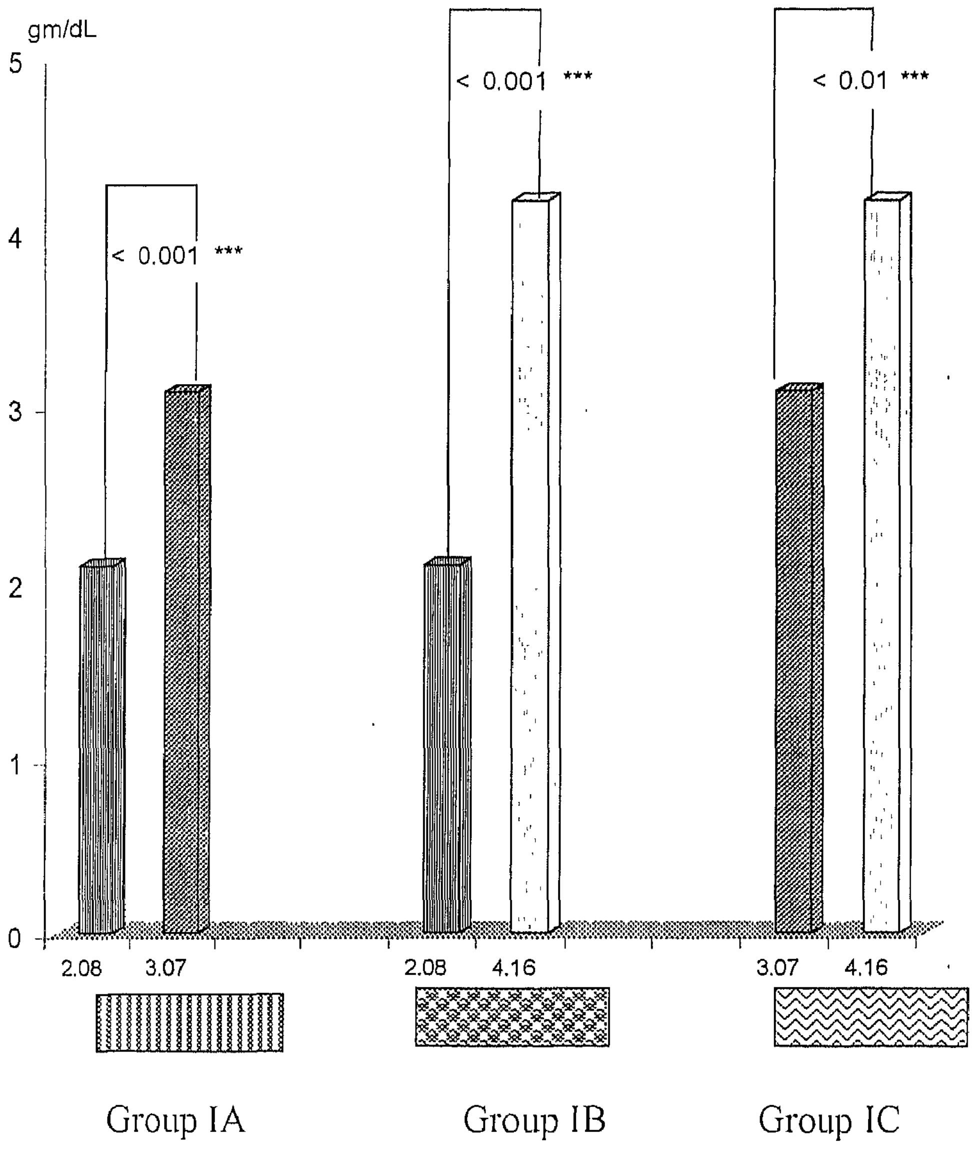
*** = Highly Significant

Figure (34): Comparison of the mean values of plasma viscosity in different patients' groups.



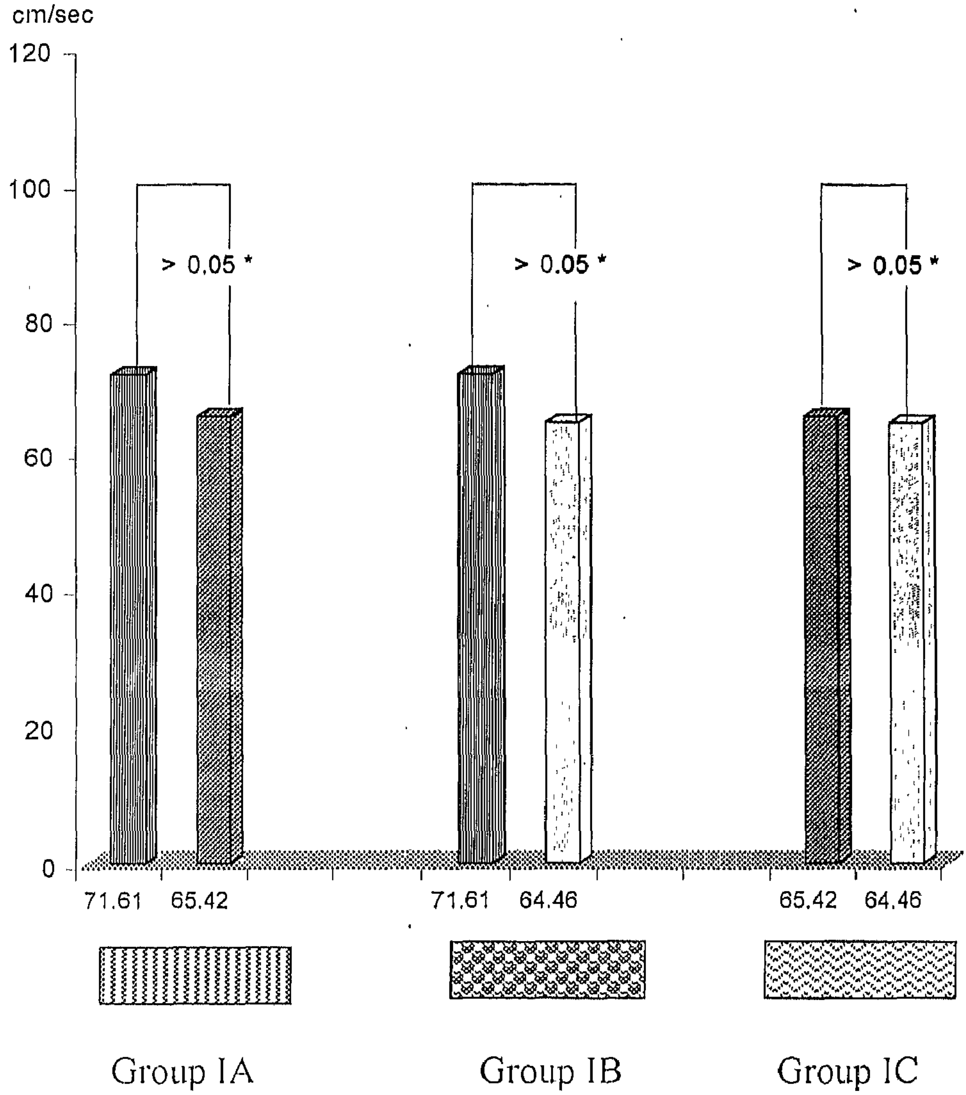
* = Non Significant
*** = Highly Significant

Figure (35): Comparison of the mean values of RBCs deformability in different patients' groups.



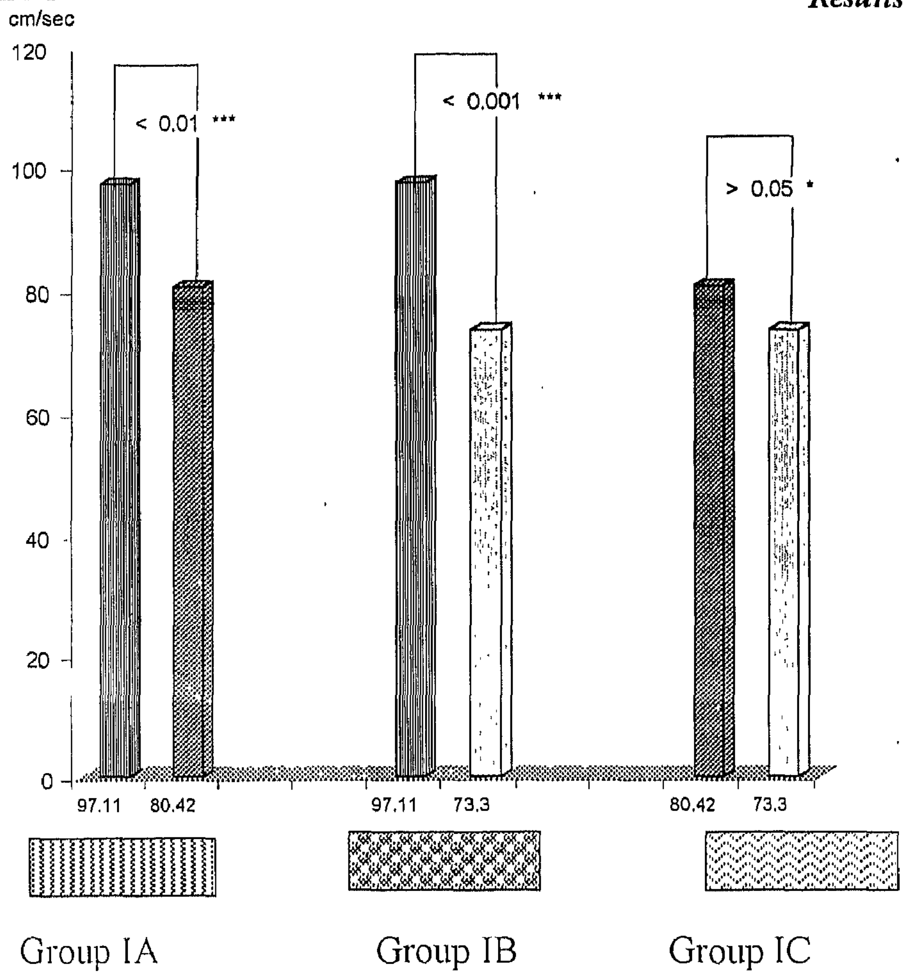
*** = Highly significant

Figure (36): Comparison of the mean values of fibrinogen in different patients' groups.



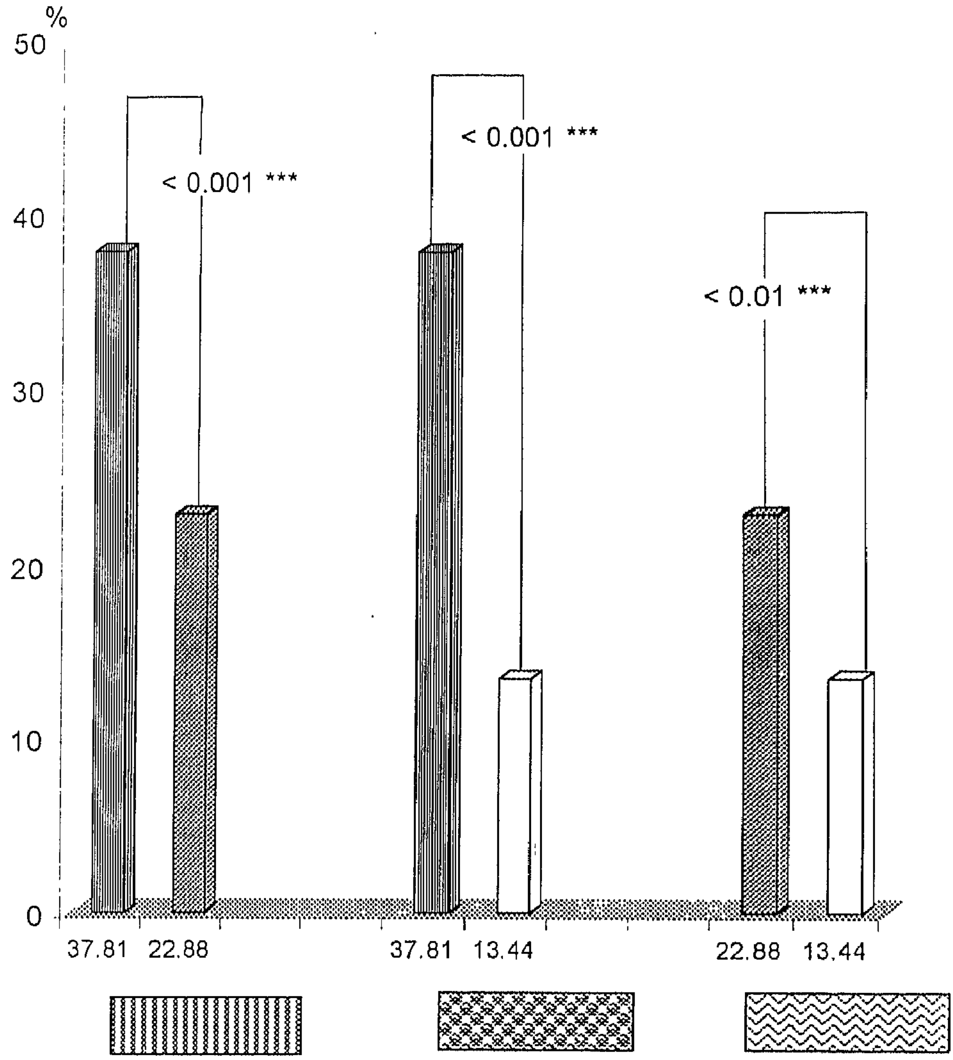
* = Non significant

Figure (37): Comparison of the mean values of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection in different patients' groups.



* = Non significant
*** = Highly significant

Figure (38): Comparison of the mean values of mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection in different patients' groups.



Group IA Group IB Group IC

*** = Highly significant

Figure (39): Comparison of the mean values of mean of vasoreactivities in different patients' groups.

Table (28): Correlation study between different clinical, Biochemical, rheological and cerebral blood flow velocities and vasoreactivity values in all patients' group.

Parameter	Hct	HbA1c	TC	HDL-C	LDL-C	TG	Plasma viscosity	RBCs Deform	Fibrinogen	MFVs of MCAs B.D	MFVs of MCAs A.D	Vaso-reactivity
D.O.D	0.29 *	0.14	0.32 *	0.09	0.30 *	0.23	0.68 *	— 0.66 *	0.78 *	— 0.31 *	— 0.60 *	— 0.83 *
Hct%	——	— 0.16	— 0.07	— 0.07	— 0.05	— 0.06	0.20	— 0.21	0.28*	— 0.08	— 0.19	— 0.22
HbA1c%	——	——	0.04	0.19	0.06	0.11	0.09	0.10	0.01	0.02	— 0.10	— 0.19

Critical value for "r" = + /- 0.2675
D.O.D = Duration of diabetes mellitus
HbA1c = Glycated hemoglobin
HDL-C = High density lipoprotein cholesterol
TG = Triglycerides.
MFVs = Mean flow velocities
MCAs = Middle cerebral arteries

* = significant correlation.
Hct = Hematocrit
TC = Total cholesterol
LDL-C = low- Density lipoprotein –cholesterol
RBCs Deform = Red blood cells deformability.
A.D. = After Diamox
B.D. = Before Diamox

Table (29): Correlation study between different Biochemical, rheological and cerebral blood flow velocities and vasoreactivity values in all patients' group.

Parameter	HDL-C	LDL-C	TG	Plasma viscosity	RBCs Deform	Fibrinogen	MFVs of MCAs B.D	MFVs of MCAs A.D.	Vaso-reactivity
TC	0.12	0.98 *	0.34 *	0.267 *	0.002	0.23	– 0.13	– 0.15	– 0.11
HDL-C	——	0.05	– 0.18	– 0.01	0.09	– 0.03	0.10	0.095	0.009
LDL-C	——	——	0.21	0.23	0.009	0.23	– 0.11	– 0.143	– 0.10
TG	——	——	——	0.27 *	– 0.11	0.08	– 0.24	– 0.17	– 0.07

Critical value for "r" = + /- 0.2675
TC = Total cholesterol
HDL-C = High density lipoprotein cholesterol
TG = Triglycerides.
MCAs = Middle cerebral arteries
MFVs = Mean flow velocities

* = significant correlation.
LDL-C = low- density lipoprotein –cholesterol
RBCs Deform = Red blood cells deformability.
A.D. = After Diamox
B.D. = Before Diamox

Table (30): Correlation study between different rheological and cerebral blood flow velocities and vasoreactivity values in all patients' group.

Parameter	RBCs Deform	Fibrinogen	MFVs of MCAs B.D	MFV of MCAs A.D.	Mean of vasoreactivity
Plasma viscosity	−0.47*	0.43*	− 0.30 *	− 0.40 *	− 0.43 *
RBCs Deform	——	− 0.62 *	0.21	0.45 *	0.63 *
Fibrinogen	——	——	− 0.34 *	− 0.59 *	− 0.70 *
MFVs of MCAs B.D.	——	——	——	0.89 *	0.22
MFVs of MCAs A.D.	——	——	——	——	0.59*

Critical value for "r" = + /- 0.2675
RBCs Deform = Red blood cells deformability.
MFVs = Mean flow velocities
MCAs = Middle cerebral arteries

* = significant correlations.
A.D. = After Diamox
B.D. = Before Diamox

Correlation study, tables (28, 29, 30): showed the following results.

- Duration of diabetes mellitus (D.O.D.): showed a significant positive correlation with hematocrit% (Hct%), TC, LDL-C, plasma viscosity, fibrinogen level and a significant inverse correlation with RBCs deformability, mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest), mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection and vasoreactivty.
- Hematocrit % (Hct %): showed a significant positive correlation with fibrinogen level.
- TC showed a significant positive correlation with LDL-C, TG and plasma viscosity.
- TG showed a significant positive correlation with plasma viscosity.
- Plasma viscosity showed a significant inverse correlation with RBCs deformability, mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest), mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection and vasoreactivity, but it showed a significant positive correlation with fibrinogen.
- RBCs deformability showed a significant inverse correlation with plasma fibrinogen but a significant positive correlation

with mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection and vasoreactivity.

- Fibrinogen showed a significant inverse correlation with mean flow velocities (MFVs of MCAs) before Diamox injection (At rest), (MFVs of MCAs) 15 minutes after Diamox injection and vasoreactivity.
- Mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Diamox injection (At rest) showed a significant positive correlation with mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection.
- Mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection showed a significant positive correlation with vasoreactivity.

Discriptive Data of Patients & Controls

Clinical data of control group.

Serial number	Sex	Age in years	Weight in kg	Percentile	Height in cm	Percentile	BMI Kg/m^2
1	M	16	60	50 th	167	25 th	21.51
2	M	6.5	26	90-97 th	122	90 th	17.46
3	F	19	67	90 th	172	90 th	22.64
4	F	8	39	97 th	121	25 th	26.63
5	F	14	50	25-50 th	142	< 3 rd	24.79
6	M	9.5	40	90-97 th	143	97 th	19.56
7	M	10	41	90-97 th	148	90 th	18.71
8	M	13	42	50 th	149	25 th	18.91
9	F	9	32	75 th	139	90 th	16.65
10	F	8	29	75 th	127	50 th	17.98
11	M	7	32	97 th	124	90 th	20.81
12	M	8	30	90 th	128	75 th	18.31
13	F	14	50	25-40 th	164	5 th	18.59
Range		6.5 – 19	26 – 67		121–172		16.65 – 26.63
$\bar{x}$	7 M	10.92	41.38		142		20.18
S.D.	6 F	± 3.88	± 12.43		± 17.53		± 2.98

$\bar{X}$ = Mean   S.D. = Standard deviation
Kg = Kilogram.   M = Male   F = Female
cm = Centimeter   BMI = Body mass index.

ıboratory data of control group.

erial umber	Hb Gm/dL	Plt ($x 10^3/mm^3$)	TLC ($x10^3/mm^3$)	Hct%	TC mg/dL	HDL-C mg /dL	LDL-C mg/dL	TG mg/dL	HbA_{1C}%	Plasma viscosity	RBCS Deform	Fibrinogen gm/dL
1	11.5	170	6.2	38.33	186	64	102	100	7.8	1.05	2.3	1.7
2	11.5	230	7.1	38.33	165	69	85	55	6.2	1.02	2.5	1.9
3	11.8	180	5.4	39.33	198	68	119	53	7.6	1.18	2	2.4
4	11.9	190	6.3	39.66	182	66	92	120	6.8	1.15	2.6	2.2
5	11.8	240	7.7	39.33	144	69	52	112	6.5	1.20	2.7	1.8
6	11.6	300	8.1	35.33	131	75	32	122	7.2	1.07	2.8	1.9
7	11.9	170	7.2	39.66	150	64	65	105	6.7	1.30	2.4	2.1
8	12.4	220	9.3	41.33	184	64	108	57	7.1	1.07	2.4	2
9	11.6	160	4.4	38.66	141	66	51	118	7.3	1.25	2.7	2.1
10	12.7	210	5.2	42.33	160	69	71	96	6.8	1.12	1.02	2.4
11	11.2	240	6.7	37.33	201	60	123	90	7.7	0.97	2.3	2.3
12	11.6	190	5.2	42	194	63	118	65	7.1	1.17	2	1.7
13	13.6	225	6.9	42.33	196	62	123	51	8.1	1.25	2.5	2.5
ange	11.2-13.6	160–300	4.4–9.3	35.33–42.33	131–201	60 – 75	32–123	51–122	6.2–8.1	0.97–1.30	1.02–2.80	1.7–2.5
$\overline{X}$	11.93	209.615	6.59	39.35	171.69	66.07	87.69	88	7.15	1.138	2.32	2.07
.D.	± 0.63	± 38.754	± 1.35	±2.07	±24.35	± 3.92	± 31.17	± 27.88	± 0.55	± 0.09	0.46	0.27

b = Hemoglobin
ct% = Hematocrit%
DL-C = Low density lipoprotein cholesterol.
G = Triglycerides.
BCs = Red blood cells

Plt = Platelets TLC = Total leukocytic count
TC = Total cholesterol
HDL-C = High density lipoprotein cholesterol.
Hb A1c% = Glycosylated hemoglobin %.
Deform = Deformability

Mean flow velocities of middle cerebral arteries (MFVs of MCAs) before and 15 minutes after Diamox injection and mean of vasoreactivities% of control group.

Serial number	MFVs of MCAs before Diamox injection cm/sec	MFVs of MCAs after Diamox injection cm/sec	Mean of vaso-reactivities %
1	75	104	39.12
2	75.5	100.5	33.1
3	76.5	101	30.37
4	81	104.5	25.92
5	74.5	97	30.18
6	79	101.5	28.44
7	72	98	36.22
8	76	109	43.42
9	71	102.5	44.36
10	81	108	33.33
11	76.5	103.5	35.3
12	77	104.5	35.71
13	79	106	34.18
Range	71 – 81	97–109	25.92–44.36
$\overline{X}$	76.46	103.07	34.58
S.D.	± 3.04	± 3.52	± 5.42

MFVs = Mean flow velocities

$\overline{X}$ = Mean

MCAs = Middle cerebral arteries

S.D. = Standard deviation

Vasoreactivity > 30% = Good reactivity

Clinical data of group IA (Duration of diabetes mellitus < 5 years).

Serial number	Sex	D.O.D. in years	Age in years	Weight in Kg	Percentile	Height in cm	Percentile	B.M.I. Kg/m^3
1	M	4	16	53	10-25 th	160	3-10 th	20.7
2	M	4.5	15	35	< 3 rd	153	3 rd	14.95
3	F	I	11	31	25 th	139	25 th	16.06
4	M	4	16	37.6	< 3 rd	165	10 th	13.81
5	F	2	17	75	25-50 th	172	90 th	25.35
6	F	I	9	28	50 th	133	50-75 th	15.82
7	M	1.5	13	40.6	25-50 th	152	50 th	17.57
8	M	4.5	16	50	10 th	167	25-50 th	17.92
9	F	4.5	17	57	50 th	155	10 th	23.72
10	F	3.5	15	59	75 th	150	< 3 rd	26.22
11	F	2.5	16	50	10-25 th	161	25 th	19.3
12	M	3	12	33	25 th	139	10-25 th	17.07
13	M	4	16	59	50 th	168	25 th	20.90
Range	7M 6F	1 – 4.5	9–17	28–75		133–172		13.81–26.22
$\bar{X}$		3.07	14.54	46.78		154.92		19.18
S.D.		± 1.33	± 2.5	± 13.87		± 12.23		± 3.98

D.O.D. = Duration of diabetes mellitus
Kg = Kilogram   cm = Centimeter
B.M.I. = Body mass index.
M = Male   F = Female

aboratory data of group IA (Duration of diabetes mellitus < 5 years).

rial umber	Hb gm/dL	Plt ($x10^3/mm^3$)	TLC ($x10^3/mm^3$)	Hct%	TC mg/dL	HDLC mg/dL	LDLC mg/dL	TG mg/dL	Hb A_{1C}%	Plasma viscosity	RBCs Deform.	Fibrinogen gm/dL
1	9.4	319	4.7	32.41	250	52	176	108	8.3	1.07	2.0	1.84
2	11.5	190	7.2	38.33	217	60	117	198	10	1.20	1.90	1.83
3	11	190	4.5	36.66	120	69	40	53	8.5	1.32	1.90	2.86
4	10.5	220	3.8	35	148	49	119	149	7	1.37	2.2	1.63
5	12.5	254	6.0	41.66	226	44	155	136	7.5	1.22	2.1	1.76
6	9.6	161	10.2	32	228	37	154	185	9	1.20	2.3	1.72
7	12.5	200	6.9	41.66	187	46	132	44	7.5	1.17	2.2	2.8
8	12	239	7.0	40	247	42	169	180	9	1.27	1.9	1.82
9	10.8	251	8.3	36	236	55	151	149	8.4	1.15	2.3	2.5
10	13	240	6.4	43.33	193	50	122	104	10	1.12	1.9	2.3
11	11.7	220	5.5	39	224	46	162	79	8.3	1.12	2.10	1.68
12	11.5	259	5.5	38.33	311	61	230	97	7.4	1.04	2.2	2.03
13	9.8	280	7.6	33.79	156	44	87	121	8.3	1.05	2.4	2.3
Range	9.4–13	161–319	3.8-10.2	32-43.33	120-311	37-69	40-230	44-198	7-10	1.04-1.37	1.9-2.4	1.63-2.86
$\overline{X}$ S.D.	11.19 ± 1.17	232.538 ± 42.266	6.43 ± 1726	37.55 ±3.62	214.85 ±46.85	50.38 ±8.88	139.76 ±46.10	123.31 ±48.80	8.4 ±0.93	1.17 ± 0.10	2.10 ± 0.17	2.08 ± 0.42

) = Hemoglobin.
.C = Total leukocytic count
: = Total cholesterol
)L-C = High density lipoprotein cholesterol
)L-C = low density lipoprotein cholesterol
A1c% = Glycated hemoglobin %

Plt = platelets
Hct% = Hematocrit%
TG = Triglycerides
Deform = Deformability
RBCs = Red blood cells.

Mean flow velocities of middle cerebral arteries (MFVs of MCAs) before and 15 minutes after Diamox injection and mean of vasoreactivities% in group IA (Duration of diabetes mellitus < 5 years).

Serial number	MFVs of MCAs before Diamox injection cm/sec	MFVs of MCAs after Diamox injection cm/sec	Mean of vaso-reactivities %
1	58	79	36.08
2	69.5	90.5	30.3
3	70	93	32.75
4	55.5	80	38.85
5	60.5	81.5	38.78
6	67	91.5	38.3
7	79	98.5	49.93
8	60.5	87	44.29
9	72	98	36.1
10	83.5	111	34.17
11	91.5	121.5	33.05
12	84	117.5	39.6
13	80	113.5	42.33
Range	55.5 – 91.5	79–121.5	30.3-49.93
$\overline{X}$	71.61	97.11	37.81
S.D.	± 11.31	± 14.53	± 5.33

$\overline{X}$ = Mean S.D. = Standard deviation

MFVs = Mean flow velocities

MCAs = Middle cerebral arteries

Vasoreactivity > 30 % = Good reactivity

Clinical data of group IB (Duration of diabetes ≥ 5-10 years.

Serial number	Sex	D.O.D. in years	Age in years	Weight in Kg	Percentile	Height in cm	Percentile	B.M.I Kg/m^2
1	M	8	16	85	> 97 th	171	25 th	29.06
2	M	5.5	13	54.5	90 th	158	75 th	21.83
3	F	6	12	45	50-75 th	142	10 th	22.31
4	F	7	14	49	50 th	151	3-10 th	21.49
5	F	8	18	68.6	90 th	165	25 –50 th	25.19
6	F	7	18	60	50-75 th	158	3-10 th	24.03
7	F	9	15	53	25-50 th	166	50-75 th	19.23
8	M	7	11	22	< 3 rd	133	10-25 th	12.43
9	M	6	15	43	10 th	160	25 th	16.79
10	M	7	17	64	50 th	173	25 th	21.4
11	M	7.5	14	54	50-75 th	152	10-25 th	23.37
12	F	7.5	14	43	25 th	149	3 rd	19.36
13	M	6.5	12	42	75 th	146	50 th	19.70
Range		5.5 – 9	11– 18	22– 85		133– 173		12.43–29.06
X	7M	7.07	14.53	52.54		155.69		21.24
S.D.	6F	±0.95	± 2.25	± 15.27		± 11.66		± 4.06

D.O.D. = Duration of diabetes mellitus
Kg = Kilogram
cm = Centimeter
B.M.I. = Body mass index. M = Male F = Female

boratory data of group IB (Duration of diabetes mellitus ≥ 5-10 years).

rial mber	Hb gm/dL	Plt ($x10^3/mm^3$)	TLC ($x10^3/mm^3$)	Hct%	TC mg/dL	HDLC mg/dL	LDLC mg/dL	TG mg/dL	HbA1c%	Plasma viscosity	RBCs Deform	Fibrinogen gm/dL
1	12.5	310	7.1	41.66	137	46	70	107	7.6	1.72	1.2	2.26
2	10.9	378	4.4	36.33	77	34	27	80	8.5	1.30	1.2	3.3
3	12.3	210	6.5	41	201	43	128	150	7.6	1.67	1.4	3.55
4	9.5	220	4.5	32.75	280	54	198	139	9.8	1.62	1.6	2.47
5	12.1	256	9.5	40.33	166	51	86	146	9.5	1.45	1.7	2.9
6	12.3	240	5.2	41	312	47	232	165	7.3	1.6	1.5	4.42
7	11.5	288	6.9	38.33	150	47	90	64	7.8	1.72	1.6	2.39
8	10.7	278	8.0	36.89	246	52	178	78	9	1.60	1.5	3.48
9	11	300	9.0	36.66	183	52	105	128	9.6	1.75	1.2	3.67
10	12.8	215	6.3	42.66	200	40	120	200	7.2	1.6	1.4	2.82
11	12	215	9.0	40	315	46	253	79	9	1.55	1.6	2.4
12	11.5	229	5.0	38.33	157	52	79	130	10	1.65	1.4	3.4
13	11.9	210	6.14	39.66	155	44	84	135	9.7	1.63	1.5	2.9
ange	9.5–12.8	210–378	4.4–9.5	32.75-42.66	77–315	34–54	27–253	64–200	7.2–10	1.3–1.75	1.2–1.7	2.26–4.42
$\overline{X}$	11.61	258.307	6.733	38.89	198.38	46.76	126.38	123.15	8.66	1.60	1.44	3.07
.D.	±0.9	±51.256	±1.733	±2.72	±71.39	±5.65	±68.46	±39.76	1.04	±0.12	±0.17	±0.63

= Hemoglobin.
C = Total leukocytic count
= Total cholesterol
L-C = High density lipoprotein cholesterol
-C = Low density lipoprotein cholesterol
A1c% = Glycated hemoglobin %
Cs = Red blood cells

Plt = Platelets
Hct% = Hematocrit%
TG = Triglycerides
Deform = Deformability.

Mean flow velocities of middle cerebral arteries (MFVs of MCAs) before and 15 minutes after Diamox injection and mean of vasoreactivities% in group IB (Duration of diabetes mellitus ≥ 5-10 years).

Serial number	MFVs of MCAs before Diamox injection cm/sec	MFVs of MCAs after Diamox injection cm/sec	Mean of vaso-reactivities%
1	73.5	88.5	20.41
2	80	98	22.58
3	73.5	92.5	25.57
4	64.5	78.5	22.23
5	71	86.5	21.89
6	55.5	66.5	20.05
7	63	69.5	9.2
8	51.5	64.5	25.53
9	77	98	27
10	53	68	28.02
11	72.5	93.5	29.09
12	63.5	76.5	20.48
13	52	65	25
Range	51.5 – 80	64.5–98	9.2–29.09
X	65.42	80.42	22.88
S.D.	± 9.98	± 12.90	± 5.09

$\overline{X}$ = Mean

S.D. = Standard deviation

MFVs = Mean flow velocities

MCAs = Middle cerebral arteries

Vasoreactivity > 30 % = Good reactivity.

Clinical data of group IC (Duration of diabetes mellitus > 10 years).

Serial number	Sex	D.O.D. in years	Age in years	Weight in Kg	Percentile	Height in cm	Percentile	B.M.I Kg/m²
1	M	15	19	69	10-25 th	163	< 3 rd	25.97
2	F	13	19	70	> 97 th	165	50 th	25.71
3	F	14	18	65	75-90 th	160	10-25 th	25.39
4	F	11	17	61	50-75 th	164	25-50 th	22.67
5	F	11	15.5	48	90 th	147	< 3 rd	22.21
6	M	12	16	53	10-25 th	158	< 3 rd	21.23
7	M	14	18	59	25-50 th	166	3 rd	21.41
8	M	13	19	56	10-25 th	171	10-25 th	19.15
9	F	11	19	54	25 th	155	3-10 th	22.47
10	F	13	17	55	25-50 th	157	10 th	22.31
11	M	14	18	55	10 th	169	75 th	19.25
12	M	14	19	64	25-50 th	171	75-90 th	21.88
13	M	11	18	57	10-25 th	168	50-75 th	20.19
Range		11 – 15	15.5–19	48–70		147–171		19.15–25.97
$\overline{X}$	7M	12.77	17.88	58.92		162.62		22.26
S.D.	6F	± 1.42	± 1.19	± 6.53		± 7.01		± 2.25

D.O.D. = Duration of diabetes mellitus
Kg = Kilogram
cm = Centimeter
B.M.I. = Body mass index.

M = Male
F = Female

boratory data of group IC (Duration of diabetes mellitus > 10 years).

ial iber	Hb gm/dL	Plt ($x10^3/mm^3$)	TLC ($x10^3/mm^3$)	Hct%	TC mg/dL	HDLC mg/dL	LDLC mg/dL	TG mg/dL	HbA_{1C}%	Plasma viscosity	RBCs Deform	Fibrinogen gm/dL
1	12	221	75	40	312	52	220	200	9.4	1.7	1.4	4.5
2	11.8	270	46	39.33	312	48	242	107	9.8	1.95	1.2	3.93
3	11.6	211	55	38.66	230	49	165	77	8.9	1.85	1.3	4.47
4	12.4	210	52	41.33	168	47	95	130	9	1.85	1.6	2.10
5	11.5	270	90	38.33	284	50	212	109	9.8	1.92	1.3	3.2
6	13.1	365	49	43.66	185	47	124	70	9.2	1.87	1.3	5.2
7	10.8	270	62	36	300	48	212	200	8.4	1.75	1.2	4.4
8	10.9	215	82	36.33	259	46	183	149	8.6	1.96	1.5	4.1
9	10.5	269	117	35	280	41	188	256	9.6	1.85	1.4	4
10	11.9	188	63	39.66	256	46	195	75	8.5	1.72	1.4	5.99
11	12.3	190	51	41	300	46	212	208	7.9	2.62	1.3	3.61
12	13.2	224	81	44	234	52	142	196	9.6	1.85	1.4	5.7
13	12	210	54	40	125	44	53	140	9	1.77	1.3	2.97
ange	10.5 – 13.2	188–365	4.6–11.7	35–44	125–312	41–52	53–242	70–256	7.9–9.8	1.7–2.62	1.2–1.6	2.1–5.99
$\bar{X}$	11.84	239.461	6.746	39.48	249.61	47.38	172.53	147.46	9.05	1.89	1.35	4.16
S.D.	±0.81	±48.519	±2.063	±2.71	±59.22	±3.04	±54.96	±59.87	±0.58	±0.23	±0.11	±1.08

= Hemoglobin.
C = Total leukocytic count
= Total cholesterol
)L-C = High density lipoprotein cholesterol
L-C = Low density lipoprotein cholesterol
A1c% = Glycated hemoglobin %
Cs = Red blood cells

Plt = Platelets
Hct% = Hematocrit%
TG = Triglycerides
Deform = Deformability

Mean flow velocities of middle cerebral arteries (MFVs of MCAs) before and 15 minutes after Diamox injection and mean of vasoreactivities% in group IC. (Duration of diabetes > 10 years).

Serial number	MFVs of MCAs before Diamox injection cm/sec	MFVs of MCAs after Diamox injection cm/sec	Mean of vaso-reactivities%
1	76	83.5	10
2	59.5	70.5	19.62
3	78.5	81	3.2
4	75	83.5	11.39
5	77	88	14.3
6	52	59	13.46
7	71.5	75	4.8
8	54	61.5	6.4
9	68.5	86.5	26.37
10	53	59	11.4
11	56	71.5	27.22
12	51.5	52	0.98
13	65.5	82	25.18
Range	51.5 – 78.5	52–88	0.98–27.22
$\overline{X}$	64.46	73.30	13.44
S.D.	± 10.51	± 12.07	± 8.84

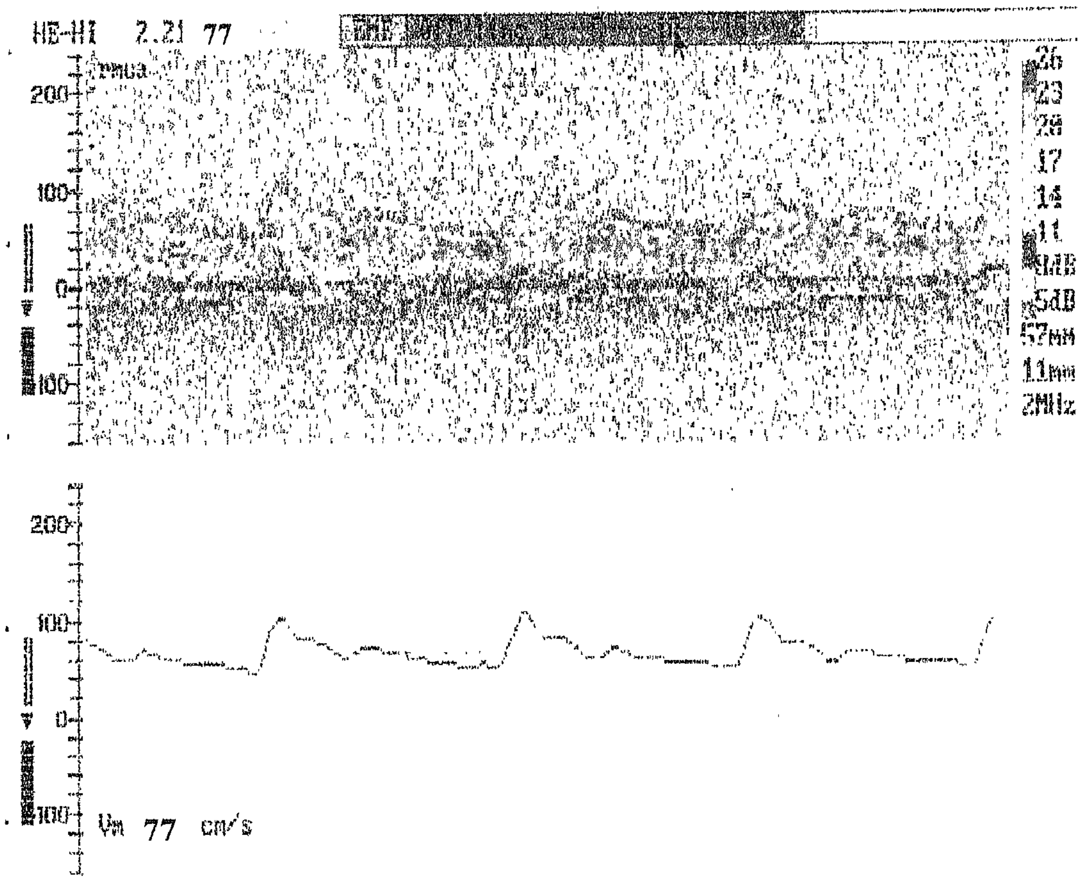
$\overline{X}$ = Mean

S.D. = Standard deviation

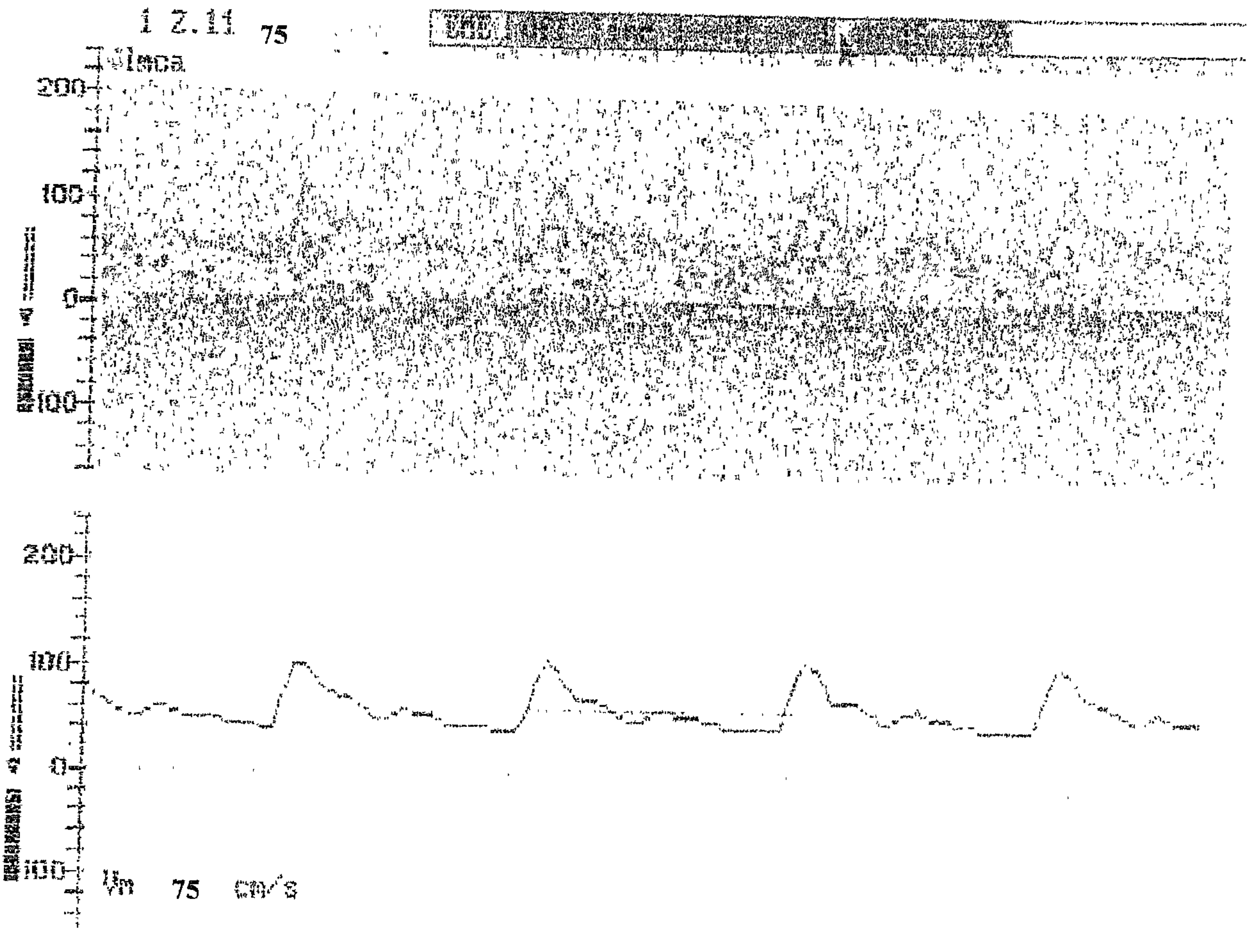
MFVs = Mean flow velocities

MCAs = Middle cerebral arteries

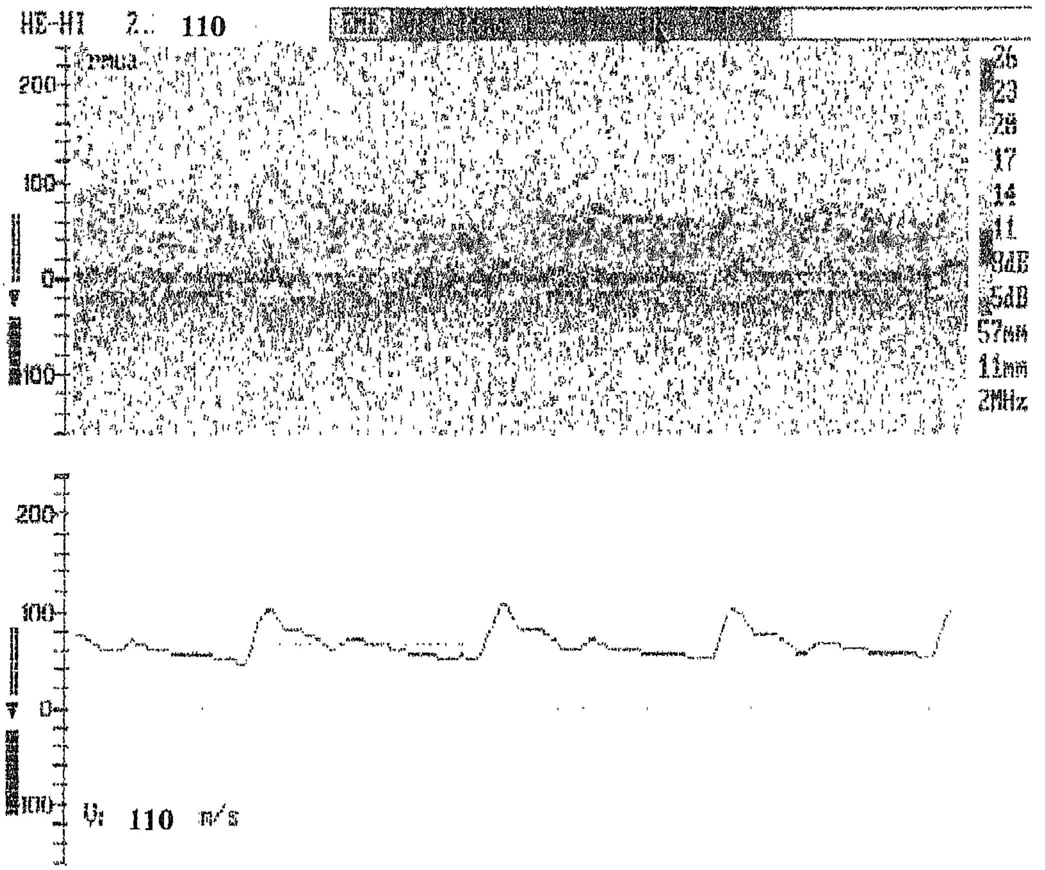
Vasoreactivity > 30 % = Good reactivity.



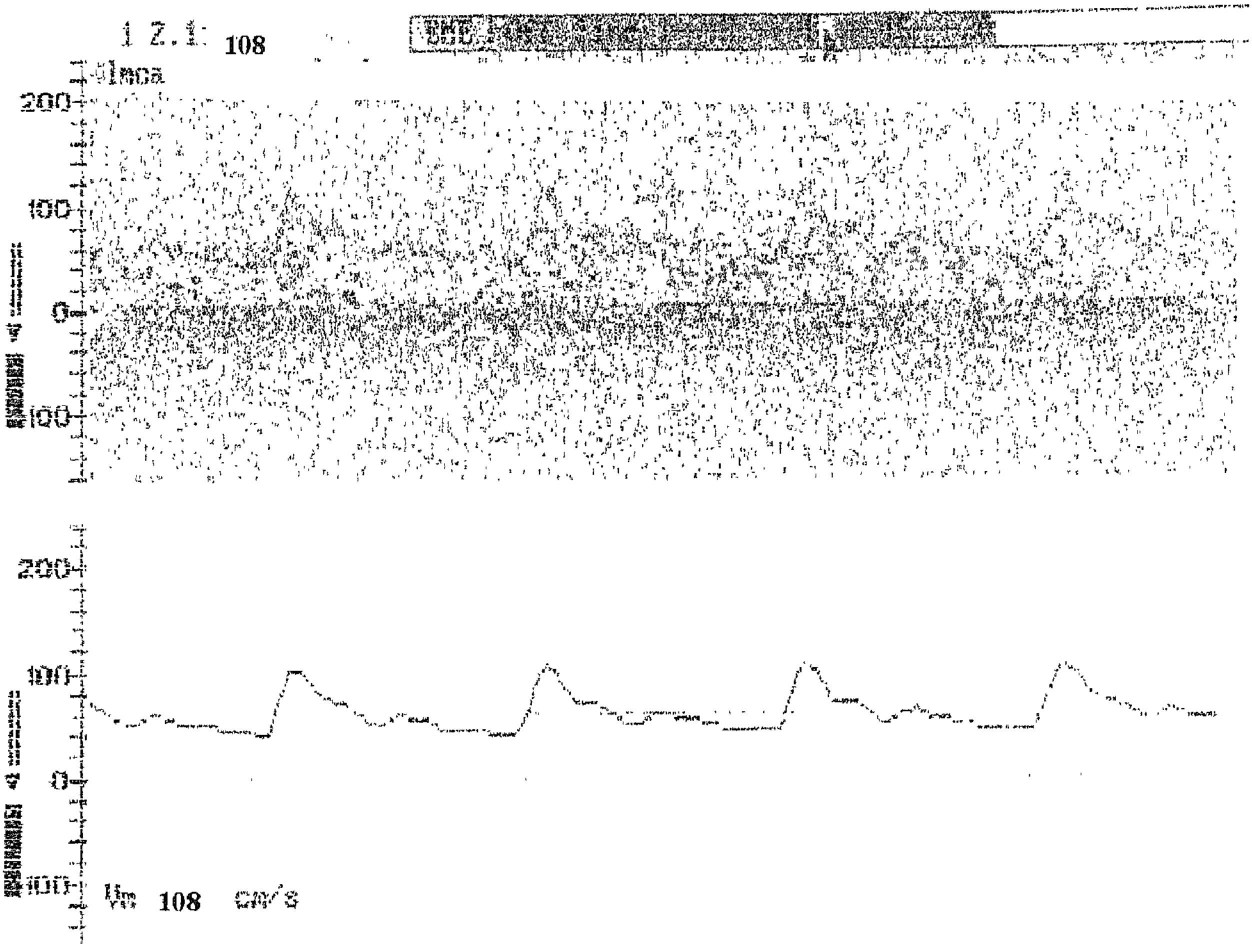
Mean flow velocity of rMCA before Diamox injection (at rest) of subject (8) of control group.



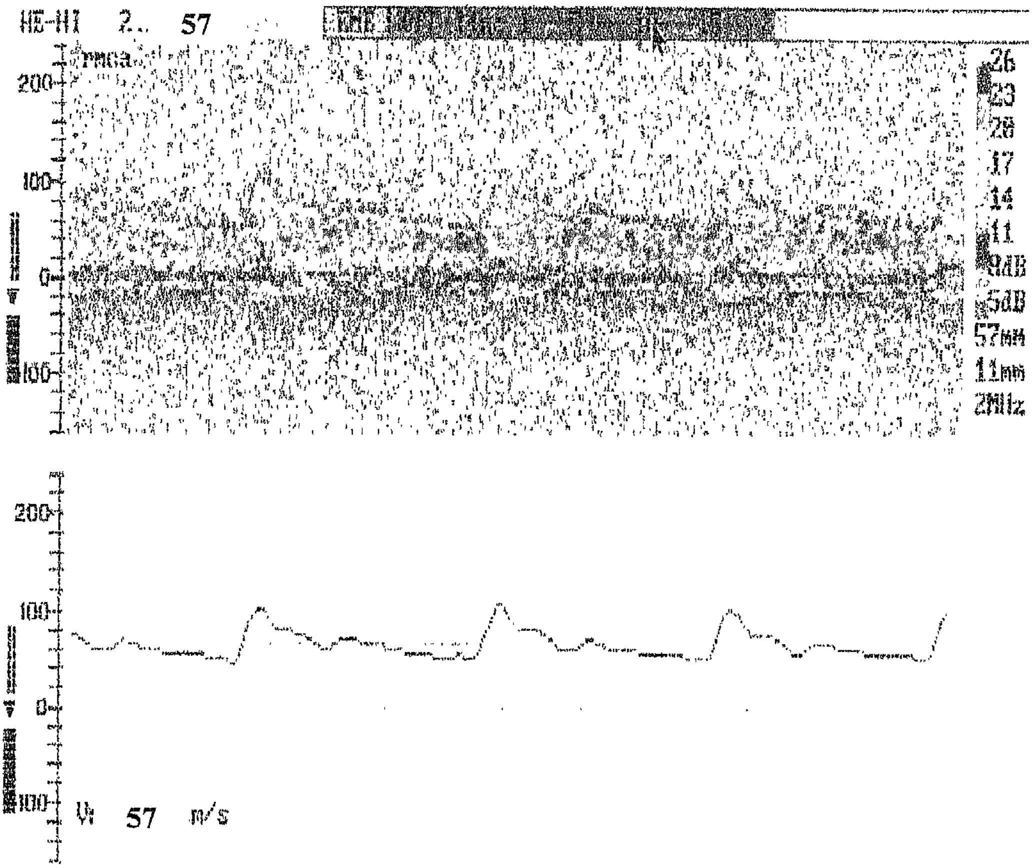
Mean flow velocity of IMCA before Diamox injection (at rest) of subject (8) of control group.



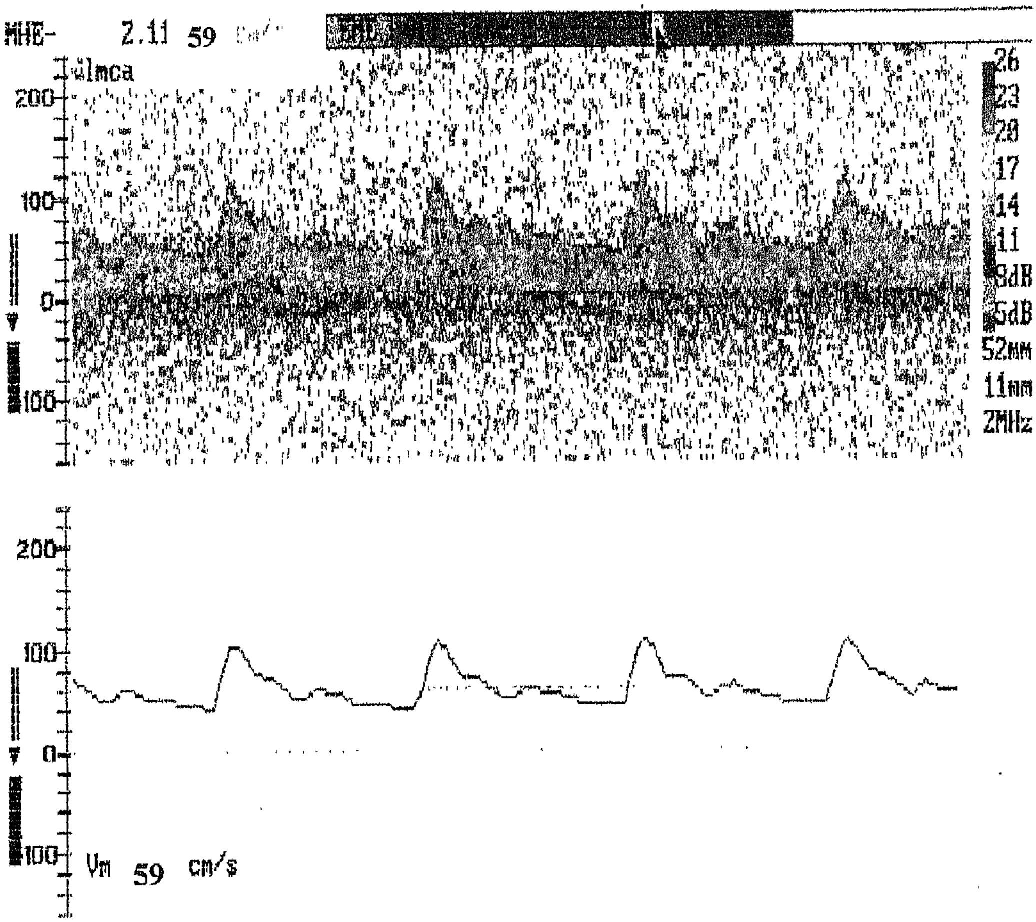
Mean flow velocity of rMCA 15 minutes after Diamox injection of subject (8) of control group.



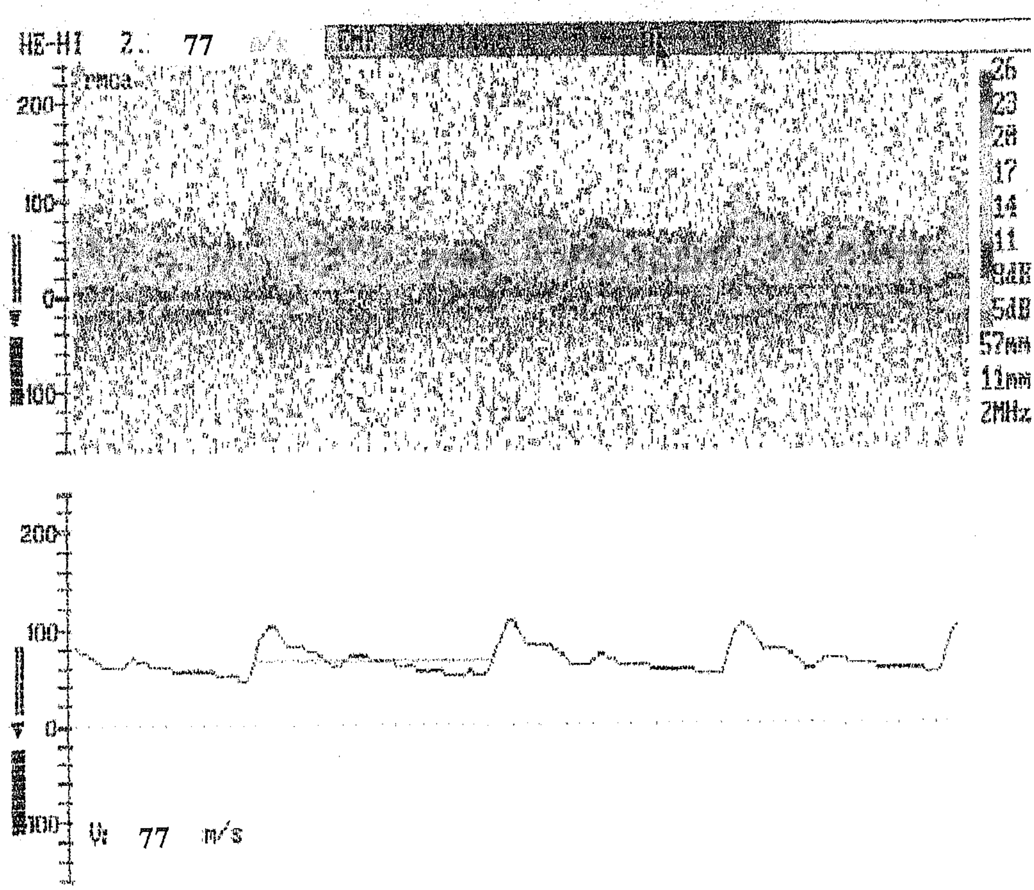
Mean flow velocity of IMCA 15 minutes after Diamox injection of subject (8) of control group.



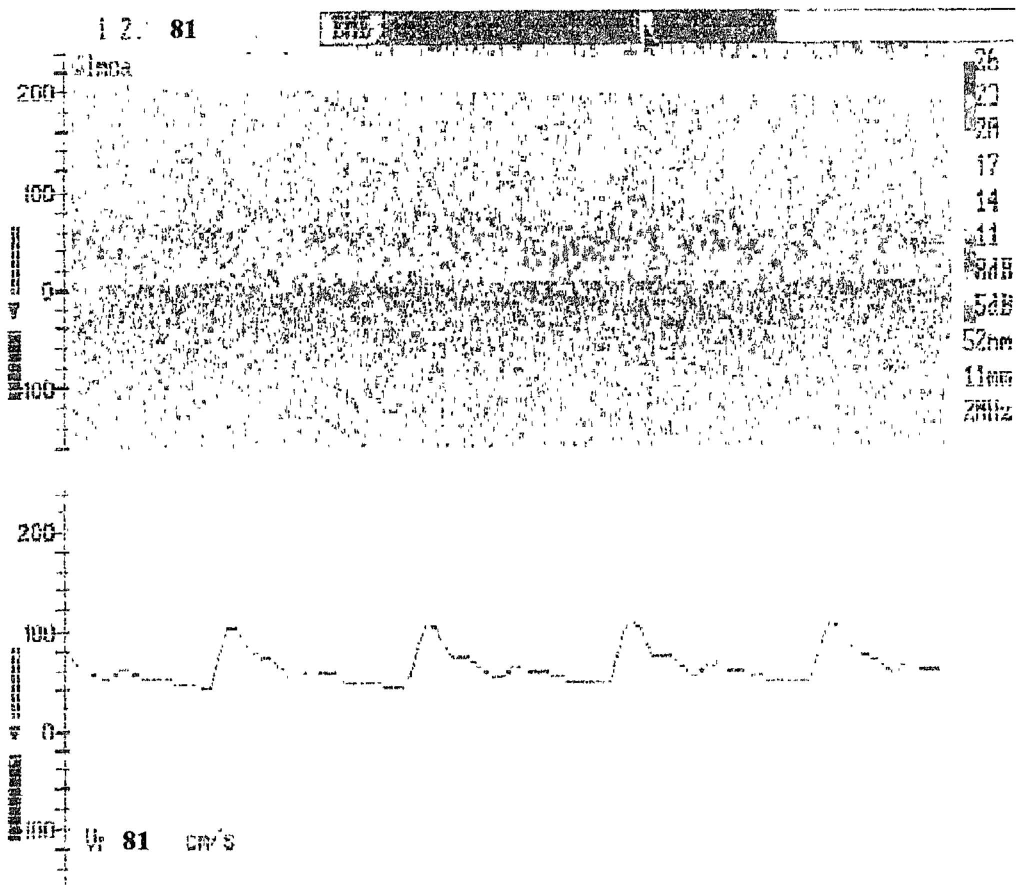
Mean flow velocity of rMCA before Diamox injection (at rest) of case (1) of group 1A.



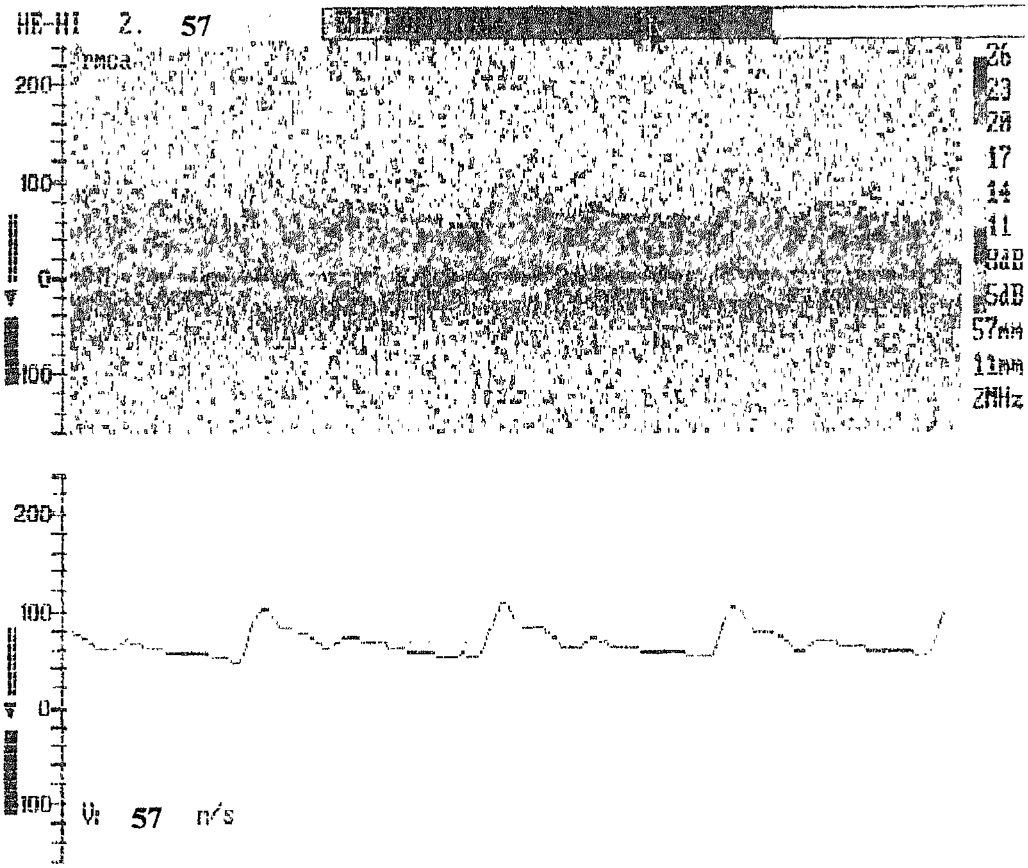
Mean flow velocity of lMCA before Diamox injection (at rest) of case (1) of group 1A.



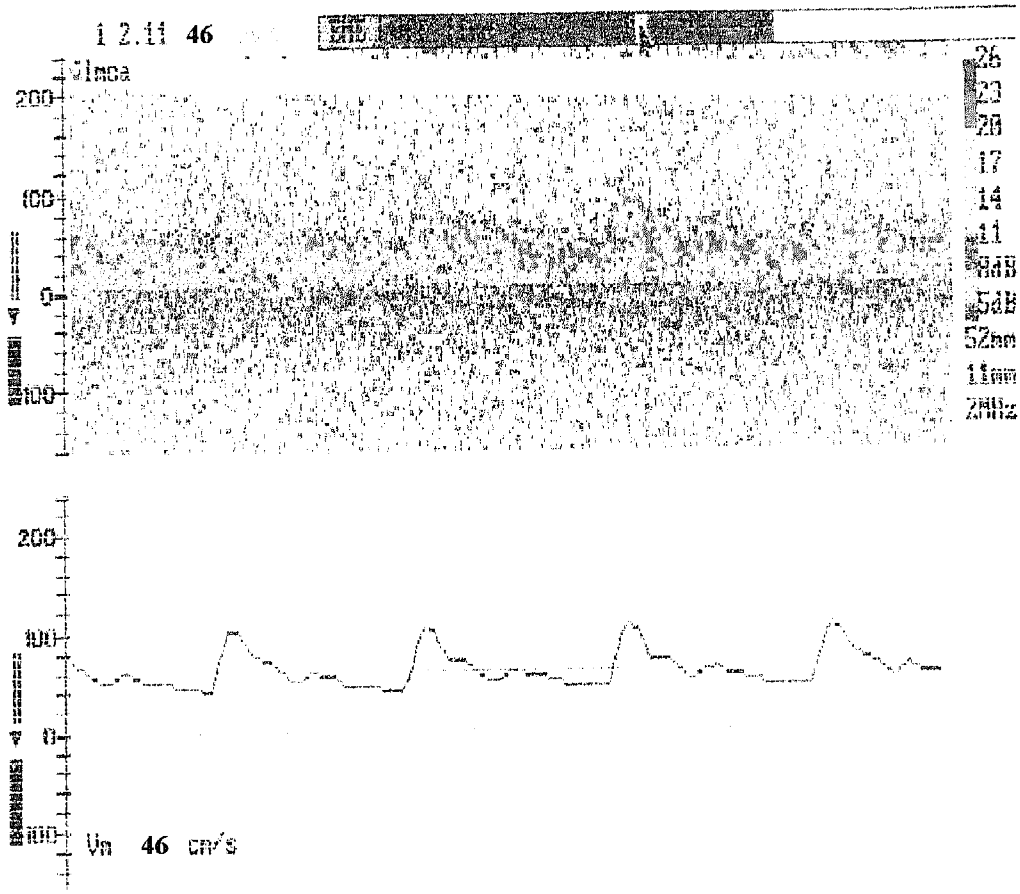
Mean flow velocity of rMCA 15 minutes after Diamox injection of case (1) of group 1A.



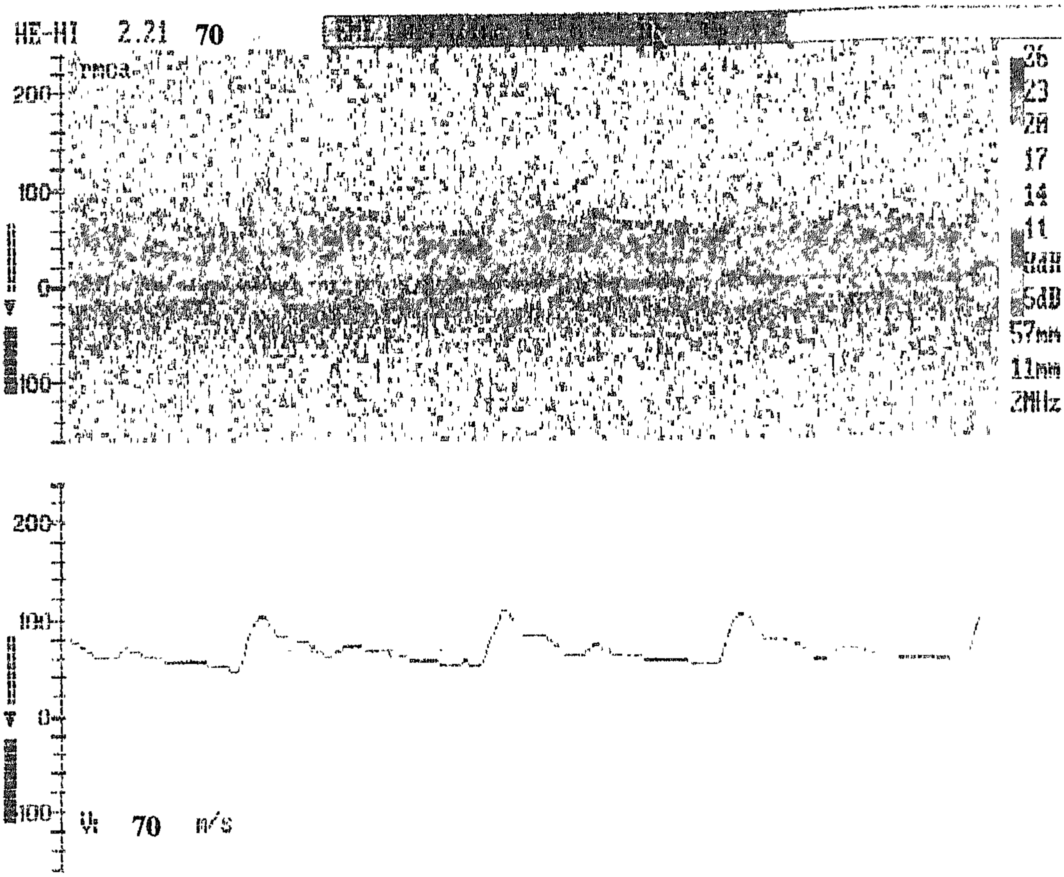
Mean flow velocity of IMCA 15 minutes after Diamox injection of case (1) of group 1A.



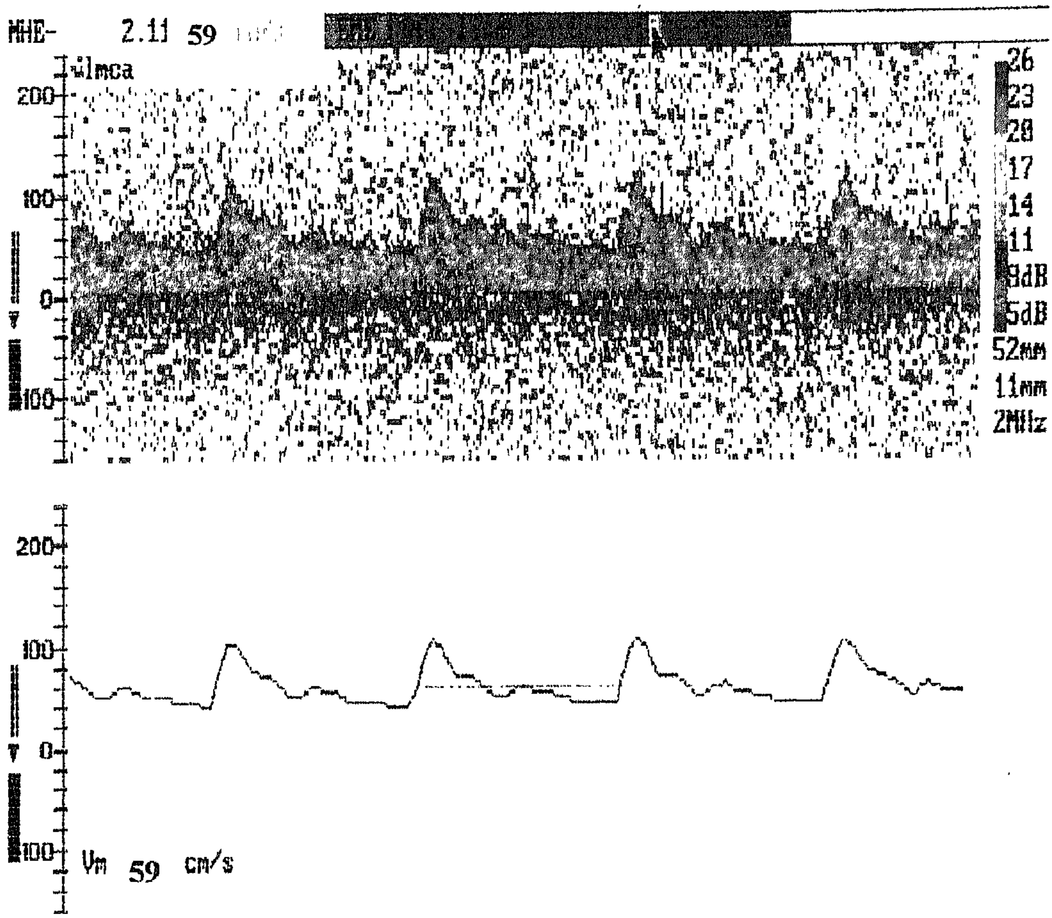
Mean flow velocity of rMCA before Diamox injection (at rest) of case (8) of group 1B.



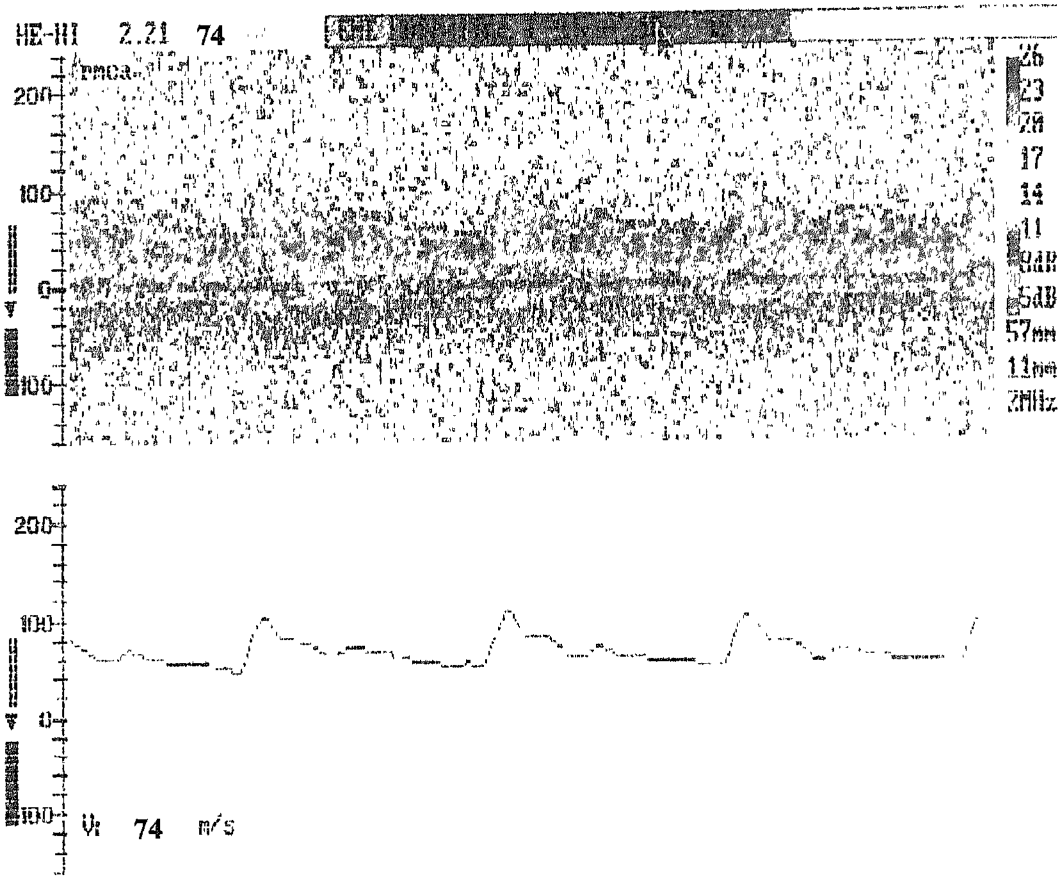
Mean flow velocity of IMCA before Diamox injection (at rest) of case (8) of group 1B.



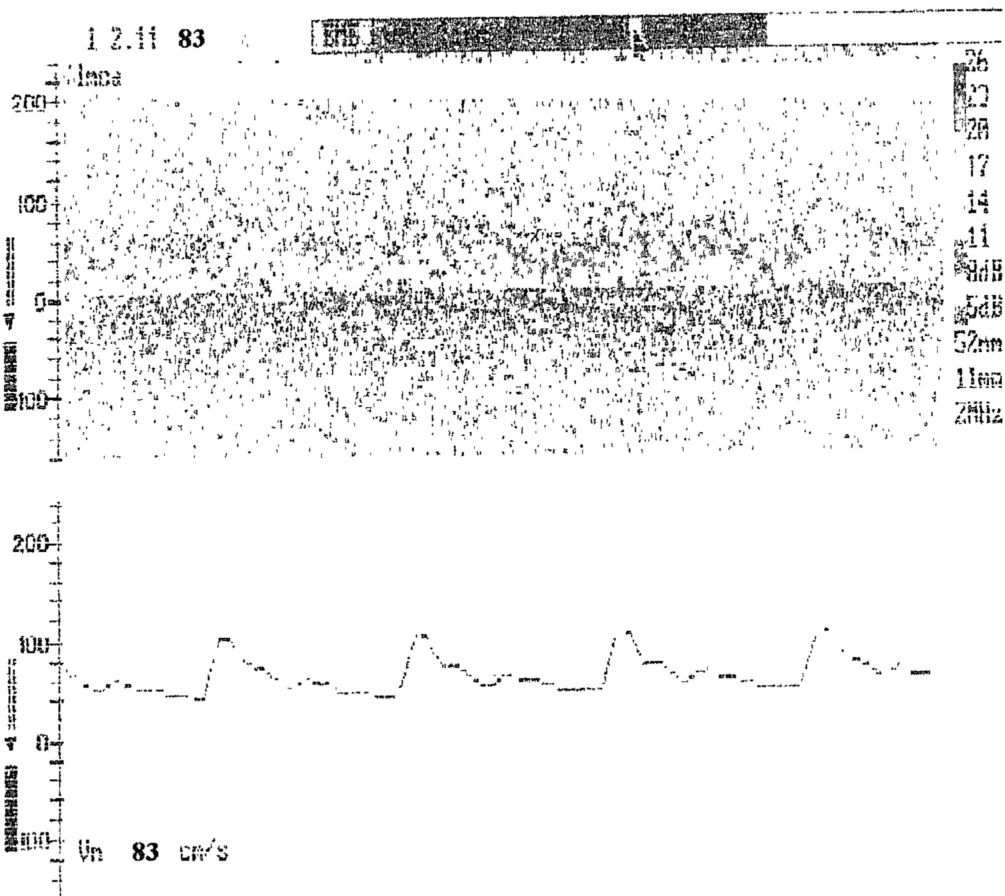
Mean flow velocity of rMCA 15 minutes after Diamox injection of case (8) of group 1B.



Mean flow velocity of lMCA 15 minutes after Diamox injection of case (8) of group 1B.



Mean flow velocity of rMCA before Diamox injection (at rest) of case (3) of group 1C.



Mean flow velocity of lMCA before Diamox injection (at rest) of case (3) of group 1C.

دراسة تدفق الدم فى المخ فى مرضى البول السكرى المعتمد على الانسولين

دراسة مقدمة من

الطبيب / هشام رمضان عبد الجواد خاطر

بكالوريوس الطب والجراحة – جامعة عين شمس (نوفمبر ١٩٨٨)

ماجستير طب الأطفال – جامعة عين شمس (مايو ١٩٩٥)

توطئة للحصول على درجة الدكتوراه فى طب الأطفال

إشـــــراف

أ.د. منى عبد القادر سالم

أستاذ طب الأطفال

كلية الطب – جامعة عين شمس

أ.د. / طريف حمزة سلام

أستاذ الباثولوجيا الاكلينيكية

كلية الطب – جامعة عين شمس

أ.د. / محمد أسامة عبد الغنى

أستاذ الأمراض النفسية والعصبية

كلية الطب – جامعة عين شمس

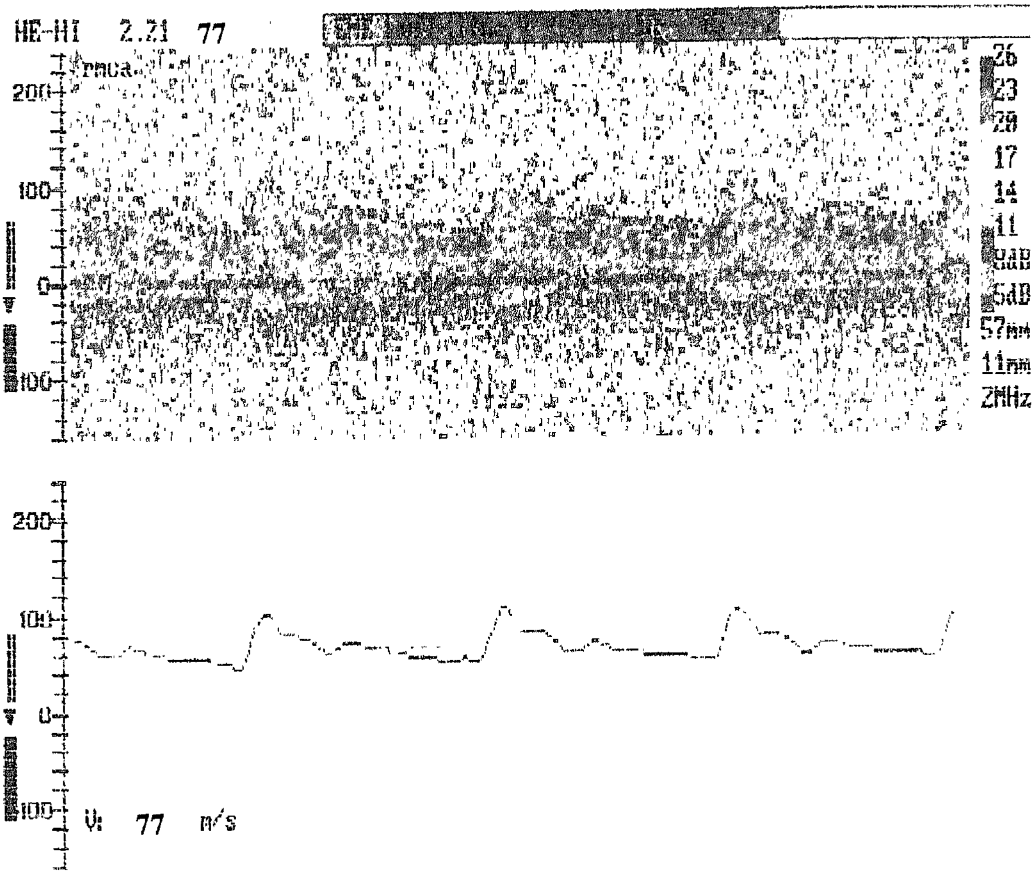
د. / نغم محمد سامى الببلاوى

مدرس طب الأطفال

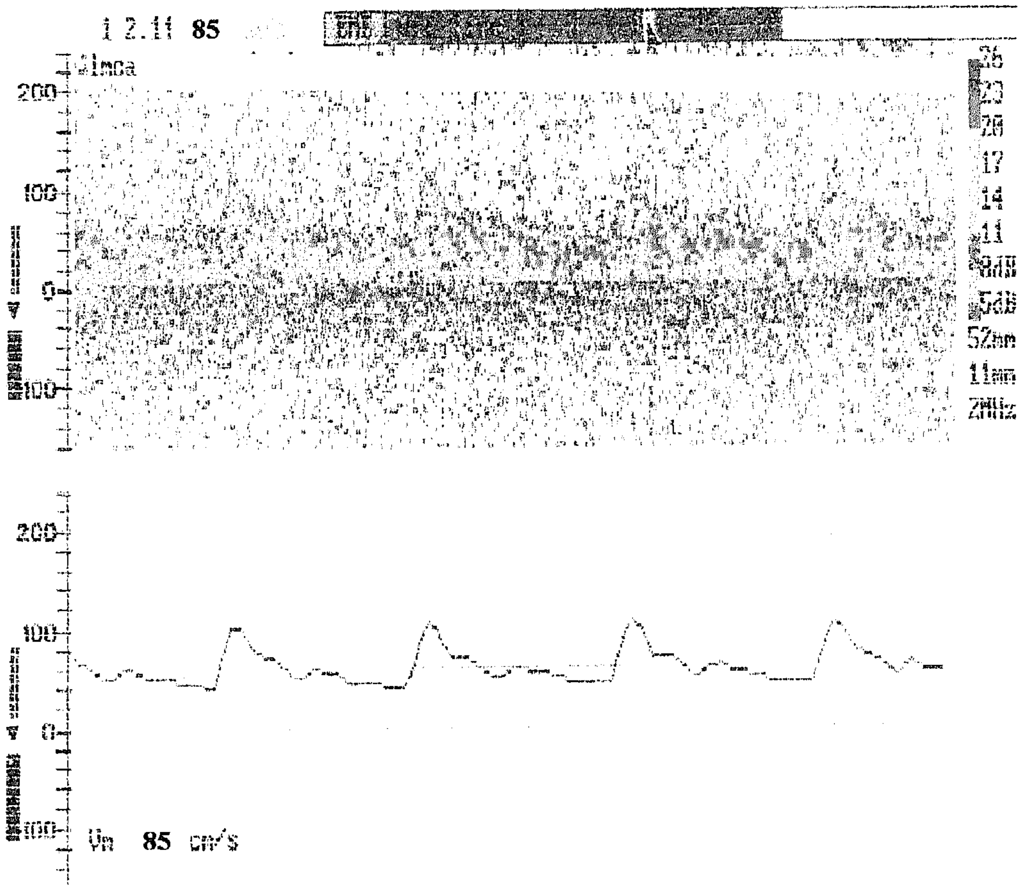
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Mean flow velocity of rMCA 15 minutes after Diamox injection)
of case (3) of group 1C.



Mean flow velocity of IMCA 15 minutes after Diamox injection of case (3) of group 1C.

Discussion

DISCUSSION

Diabetes Mellitus is one of the leading risk factors for cerebrovascular diseases. The incidence of ischemic stroke in diabetic patients has been reported to be two to six folds higher than in non diabetic subjects **(Burchfiel et al., 1994)** and patients with diabetes tend to have a worse outcome after ischemic stroke **(Biessels et al., 1994).**

Aslid et al. (1982) discovered that with 2 MHz pulsed doppler probe, it was possible to measure blood flow velocity in the basal intracranial arteries. Certain parts of the skull (So "called acoustic windows"), especially the foramen magnum and parts of the temporal bone allow the assessment of blood flow in the intracranial segments of the carotid artery, in the proximal parts of the middle and anterior cerebral arteries and in all of the basilar and the proximal parts of the posterior cerebral arteries. In recent years, the use of TCD after stimulation with Acetazolamide (Diamox) has been shown to be sensitive for the detection of reduced cerebral vasoreactivity in different diseases **(American Academy of Neurology, 1990).**

This evoked the interest to study the haemodynamic changes that might contribute to cerebrovascular disorders in patients with

type-I diabetes. The results of the current study clearly demonstrated that, changes in cerebral blood flow and cerebral vasoreactivity, haemorheological changes and lipid profile changes do occur.

In our study, the cerebral vasoreactivity was significantly low in those with a disease duration more than 5 years (group IB and IC) compared to both controls and those with a disease duration less than 5 years (group IA), but it did not show significant difference in those with a disease duration less than 5 years (group IA) compared to controls.

Of interest in this study is that, the cerebral vasoreactivity showed a significant inverse correlation with diabetes duration, plasma viscosity and fibrinogen, and a significant positive correlation with RBCs deformability.

Our study is in agreement with **Dandona et al. (1978)** in their study on 59 diabetics as they reported a significant reduction in basal cerebral blood flow (At rest) as age increases and a significant reduction of cerebral vasoreactivity in 26 patients and this impaired cerebrovasuclar reactivity involved those with long term disease and some of the newly diagnosed cases.

Also this study goes with **Croughell et al. (1990)** in their study on eleven type-1 diabetic patients versus twelve non diabetic patients, all are facing CPB for coronary atherosclerosis. They detected impaired cerebral auto-regulation at hypothermic state in diabetics facing CPB.

Also, **Rodriguez et al. (1993)** in their study on 20 type-I diabetics they found a significant inverse correlation between basal cerebral blood flow (At rest) and diabetes duration which is the same in our study and found no significant correlation between cerebrovascular reactivity and glycemic control which is the same in our study but failed to detect a linear correlation between cerebral vasoreactivity and diabetes duration which is against our study which could be due to the relatively small sized sample of patients they examined compared to our group.

At the same time, we are in agreement with **Fulsedi et al. (1997)** who examined cerebral blood flow and cerebral vasoreactivity in type-1 diabetics as they found no significant change in cerebrovascular reactivity in those with a disease duration less than 10 years, but they found impaired cerebrovascular reactivity in patients with a disease duration more than 10 years compared to both controls and group of short duration and this impaired cerebrovascular reactivity is inversely correlating with diabetes duration. Meanwhile, they detected no significant

change in basal cerebral blood flow in the two groups of patients compared to controls or to each others. This disagrees with our study as we found an earlier decrease in basal cerebral blood flow and cerebrovascular reactivity in type-1 diabetics with a disease duration ≥ 5-10 years (group IB) compared to controls. This may be due to difference in patients selection in the two studied populations.

This impairment of cerebral reactivity and cerebral blood flow could be due to pathological changes of the small vessels in the form of microatheroma formation, lipid and hyaline deposits and thickening of the basement membrane **(Lorenzi and Cagliero, 1991; Fulsdi et al., 1997)** which is not directly related to glycemic control as evidenced by the absence of a significant correlation between basal cerebral blood flow and vasoreactivity and HbA1c% but could be related to disease duration which is supported by the positive correlation between basal cerebral blood flow and cerebral vasoreactivity with disease duration.

These pathological alterations might explain the slower and less intensive vasodilatory response of the resistance cerebral vessels after administration of Acetazolamide which are responsible for the vasodilatory reactions of the brain. So impaired cerebrovascular reactivity probably refers to microangiopathic changes of the brain resistance vessels and these changes are part of

the generalized microangiopathy caused by diabetes (**Fulsedi et al., 1997**).

Also the disturbed haemorheological parameters (plasma viscosity, fibrinogen and RBCs deformablity) could be important contributing factors that may accelerate the cerebral microangiopathic and macroangiopathic changes in type-1 diabetics (**Zimmermann et al., 1996**).

In our study, cerebrovascular reactivity showed a significant inverse correlation with plasma viscosity and fibrinogen and a significant positive correlation with RBCs deformability. Also, the basal cerebral blood flow showed a significant inverse correlation with plasma viscosity and fibrinogen. These rheological properties of blood are important in determining blood flow in large and small vessels (**Skalak and Chien, 1981**) as in the microcirculation, the major rheological determinants are plasma viscosity, erythrocyte aggregation and erythrocyte deformability (**Zimmermann et al., 1996**).

Changes in these rheological parameters promote capillary stasis leading to local hypoxia, therefore the observed rheological alterations may contribute to the microvascular complications in these diabetic patients (**Zimmermann et al., 1996**).

Fibrinogen level in our study was significantly high in patients with a disease duration more than 5 years (group IB and IC) compared to both controls and those with a disease duration less than 5 years (group IA). But its mean value showed no statistically significant difference in those with a disease duration less than 5 years (group IA) compared to controls.

Also, fibrinogen level showed a significant positive correlation with diabetes duration, plasma viscosity and a significant inverse correlation with basal cerebral blood flow and vasoreactivity.

We are in agreement with many authors who reported increased fibrinogen level in type-1 diabetics as **Fulsedi et al. (1997)** who documented a significant increase in fibrinogen level in type-1 diabetic patients with a disease duration more than 10 years compared to both controls and those of short term diabetes and this increased fibrinogen was inversely correlating with cerebral vasoreactivity and **Zimmermann et al.** (1996) who reported a significant increase in plasma fibrinogen concentration in type-1 diabetic patients with micro-albuminuria and those with overt nephropathy with a disease duration more than 15 years.

Meanwhile, our result is in agreement with **Zimmerman** et **al.** (1996) **and Sandhagen et al.** (1997) who found a strong

positive correlation between plasma viscosity and fibrinogen level and **Abdul Ghani et al. (1990-b)** who found a highly significant inverse correlation between fibrinogen and CBF.

As regard RBCs deformability in our study, it was significantly low in type-1 diabetics with a disease duration more 5 years (group IB and IC) compared to both controls and those with a disease duration less than 5 years. But its mean value showed no statistically significant difference in those with a disease duration less than 5 years (group IA) compared to controls.

Also, in our study, RBCs deformability showed a significant inverse correlation with fibrinogen, plasma viscosity and diabetes duration and a significant positive correlation with MFVs of MCAs 15 minutes after diamox injection and cerebral vasoreactivity.

We are in agreement with many investigators who previously documented no significant change in RBCs deformability and fibrinogen level in short term type-1 diabetics with a disease duration less than 5 years **(Sandhagen et al., 1997)** and also compatible with other investigators who proved impaired RBCs deformability in long term type-1 diabetic patients especially those with poor glycemic control **(Juhan et al.; 1982 Bareford et al., 1986 and Linderkamp et al., 1999).**

Impaired RBCs deformability might be due to abnormal erythrocyte membrane properties in diabetic Patients including increased glycated proteins, lipid peroxidation, and increased intracellular calcium concentration **(Alexiewicz et al., 1995)** as impaired RBCs deformability may further diminish microvascular flow at low perfusion pressure **(Linderkamp et al., 1999).**

Concerning plasma viscosity in our study, it was significantly high in those with a disease duration more than 5 years (group IB and IC) compared to both controls and those with a disease duration less than 5 years (group IA). But its mean value showed no statistically significant difference in those with a disease duration less than 5 years (group IA) compared to controls.

At the same time, plasma viscosity showed a significant positive correlation with diabetes duration and a significant inverse correlation with basal cerebral blood flow velocity and cerebral vasoreactivity.

Our results are in agreement with **Sandhagen et al.** (1997) who found no significant change in plasma viscosity and erythrocyte aggregation in short term type-1 diabetics with a disease duration less than 5 years and **Abdul Ghani et al.** (1990-a) who found a significant increase in plasma viscosity and decrease in RBCs filterability (Deformability) in diabetic children and with

Zimmermann et al. (1996) who found a significant increase in plasma viscosity in type-1 diabetic patients with overt nephropathy. Also, we are in agreement with **Abdul Ghani et al. (1990-b)** who found a significant inverse correlation between plasma viscosity and CBF.

These rheological disturbances (including increased fibrinogen and plasma viscosity and decreased RBCs deformability) in our study could explain the early decrease in basal cerebral blood flow and impaired cerebrovascular reactivity in those with a disease duration ≥ 5-10 years (group IB) compared to healthy controls.

As regard hematocrit% in our study, it showed no statistically significant difference in all diabetic subgroups compared to either controls or each other's. Also, its value showed no significant correlation with basal cerebral blood flow and cerebrovascular reactivity and any of the haemorheological parameters except a weak significant positive correlation with fibrinogen.

We are in agreement with **Zimmermann et al. (1996)** in their study on long term type-1 diabetics with a disease duration more than 15 years, who found no significant change in Hct% compared to controls and **Khodabanholu et al. (1998)** as they

found no significant difference of Hct% in type-1 diabetic patients during periods of normoglycemia and hyperglycemia.

But our results disagree with **Khalifa et al. (1990)** who found a significant increase in hemoglobin and Hct% in IDDM patients compared to controls and they explained this increased hemotocrit value by the higher serum osmolarity which was found in their IDDM patients. Meanwhile **Sandhagen et al. (1997)** found that Hct% was significantly high in IDDM patients with a disease duration more than 5 years compared to controls in contrast to our results and they postulated that, increased Hct% in diabetic patients could be compensatory for a reduction in oxygen transport capacity due to increased hemoglobin glycosylation.

And also disagreeing with **Linderkamp et al. (1999)** who reported a higher Hct% in the untreated type-1 diabetics and those treated for 5 to 10 years compared to controls.

As regard lipid profile TC, LDL-C, and TG were significantly high and HDL-C was low in all subgroups of type-1 diabetics compared to controls, however TC showed no significant difference in those with a disease duration ranging between 5 and 10 years (group IB) compared to controls.

We are in agreement with many investigators who stated that LDL, VLDL, (VLDL= Triglycerides rich) levels are increased and HDL-C level are depressed in poorly controlled diabetics (**Nikkla, 1981.; Taskinen, 1992 and Stern, 1996**) and also compatible with **Dullaart. (1995) and Fahiem** (1995) who stated that, TG, TC and LDL-C are increased and HDL-C are low in poorly controlled diabetics and stated that increased LDL-C and TG are associated with vascular disease (**Dullaart, 1995**).

On the contrary, **Rafaat. (1993)** reported that TC and LDL-C concentrations were similar among Egyptian diabetic children when compared to non-diabetics and **Ahmed. (1995)** found increased HDL-C and similar levels of LDL-C among diabetic subject compared to controls.

This discrepancy between these findings and those in our study could reflect differences in patients selection, number of studied subjects, changes in dietary patterns and/or degree of metabolic control.

Modified low density lipoproteins (LDL) including oxidized LDL and advanced glycation end products-low density lipoprotiens (AGE-LDL) and these chemically reactive circulating AGE–peptide contribute to diabetic vascular .disease by reattaching to susceptible target proteins both inside and outside the vasculature

and this process accelerates vascular pathology in diabetics and this vascular pathology increases the risk of stroke and may lead to haemodynamic alterations which are reflected in the form of regional alterations in cerebral blood flow in addition to cerebral vasoreactivity (**Makita et al., 1996**).

Summary and Conclusion

SUMMARY & CONCLUSION

Diabetes mellitus is considered to be the most common endocrine metabolic disorder in childhood. The increasing survival of children with type-1 diabetes mellitus as a result of improved medical care is associated with an increased incidence of complications, especially vascular complications.

Haemorheologic abnormalities have been reported in diabetes mellitus. Many studies have reported an alteration in blood rheology and its impact on the cerebral blood flow and cerebrovascular reactivity.

This study included 39 type-1 diabetic children and adolescents as well as 13 age and sex matched healthy children and adolescents serving as controls. Type-1 diabetic patients were further subdivided into three subgroups; group IA which included 13 diabetic patients with a disease duration less than 5 years; group IB which included 13 diabetic patients with a disease duration ranging between 5 and 10 years and group 1C which included 15 diabetic patients with a disease duration more than 10 years.

All patients and controls were subjected to TCD-Diamox examination to measure blood flow of the middle cerebral arteries and cerebrovascular reactivity. Also plasma viscosity was measured using capillary tube viscometery (Oswald technique), RBCs deformability was measured using modified filtration technique, fibrinogen was measured using thrombin time, hematocrit% was assayed, glycated hemoglobin% was measured by Quick column procedure, lipid profile parameters (TC, HDL-C, LDL-C, TG), all were measured as follows, TC by (Precipitation technique), TG by (Colorimetric enzymatic assay), LDL-C was estimated by Friedwald's formula and HDL-C was measured by (Precipitation technique).

The results of the concurrent study clearly demonstrated that, HbA1c% was significantly high in all subgroups of type-1 diabetics compared to controls, but Hct% showed no significant change in all subgroups of type-1 diabetics compared to controls. However, plasma viscosity and fibrinogen level were significantly high in type-1 diabetics with a disease duration more than 5 years (group IB and IC) compared to either controls or diabetics with a disease duration less than 5 years (group IA) but RBCs deformability was significantly low in those with a disease duration more than 5 years (Group IB and IC) compared to either controls or those with a disease duration less than 5 years (group IA).

Also, lipid profile (TC, LDL-C, TG) were significantly high and HDL-C was significantly low in all type-1 diabetics in different subgroups compared to controls except the mean value of TC which showed no significant change in those with a disease duration ranging between 5 and 10 years (group IB) compared to controls.

Also, the mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before Acetazolamide (Diamox) injection and 15 minutes after its injection and mean value of cerebral vasoreactivity in type-1 diabetics with a disease duration more than 5 years (group 1B and 1C) were significantly low compared to controls.

This study showed that, diabetes duration had a significant positive correlation with Hct%, TC, LDL-C, plasma viscosity, fibrinogen and a significant inverse correlation with RBCs deformability, (MFVs of MCAs) before and 15 minutes after Diamox injection and mean of vasoreactivity.

Plasma viscosity showed a significant positive correlation with plasma fibrinogen and a significant inverse correlation with RBCs deformability, mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before and 15 minutes after Diamox injection and vasoreactivity.

Also, RBCs deformability showed a significant positive correlation with mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) 15 minutes after Diamox injection and cerebral vasoreactivity.

Meanwhile, fibrinogen level showed a significant inverse correlation with mean value of mean flow velocities of middle cerebral arteries (MFVs of MCAs) before and 15 minutes after Diamox injection and vasoreactivity.

In conclusion, our study clearly demonstrated significant alterations in basal cerebral blood flow and cerebrovascular reactivity and haemorheological parameters including fibrinogen, plasma viscosity and RBCs deformability, Hct% and lipid profile in type-1 diabetics. All these changes would contribute to the high incidence of early vascular complications in diabetic children and adolescents. The need to monitor these changes and to try to modify them early in the course of the disease is clearly validated and justified.

Recommendations

Recommendations:

1- Early monitoring and proper glycemic control is mandatory in type-1 diabetics to delay such abnormalities including the disturbed lipid profile.

2- Also non-invasive testing of the cerebral vascular complications using TCD may appear to be an important tool for a screening and prevention program of diabetic complications.

3- Further studies on large scale of patients are recommended for further evaluation of the beneficial role of this procedure.

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Arabic Summary

كرات الدم الحمراء وكذلك سرعة تدفق الدم فى شرايين المخ قبل حقن عقار الدياموكس وبعد ١٥ دقيقة من حقن هذا العقار.

٢- كذلك وجد أن لزوجة البلازما تتناسب تناسبا عكسيا مع معامل تحور كرات الدم الحمراء وسرعة تدفق الدم فى شرايين المخ قبل حقن عقار الدياموكس وبعد ١٥ دقيقة من حقن هذا العقار بينا أظهرت هذه الدراسة تناسبا طرديا بين لزوجة البلازما ومادة الفيبرينوجين.

٣- وكذلك أظهرت هذه الدراسة وجود علاقة تناسبية طردية بين معامل تحور كرات الدم الحمراء و سرعة تدفق الدم فى شرايين المخ بعد حقن عقار الدياموكس بخمسة عشرة دقيقة .

الاستنتاجات والتوصيات :

لقد ظهر جليا من هذه الدراسة أن الاطفال والبالغين الذين يعانون من مرض البول السكرى المعتمد على الانسولين تحدث لهم تغيرات فى سيولة الدم وكذلك فى صورة الدهون والدهون البروتينية التى تنعكس بصورة واضحة على سرعة تدفق الدم فى شرايين المخ والتى قد تؤدى إلى حدوث مضاعفات خطيرة بالمخ بمرضى السكر.

ولذلك ننصح بمزيد من القاء الضوء على هذه التغيرات وكذلك الفحص المستمر والمنتظم لهؤلاء المرض وعملية انضباط مستوى السكر بالدم لمحاولة منع هذه التغيرات ذات الانعكاسات الخطيرة على المخ .

وكذلك من الممكن استخدام جهاز الدوبلر لقياس سرعة تدفق الدم فى مرضى البول السكرى لاكتشاف اى تغيرات فى سريان الدم بالمخ مبكرا لمنع حدوث مثل هذه المضاعفات.

وقد أظهرت هذه الدراسة النتائج التالية أن نسبة الهيموجلوبين المسكر قد زادت زيادة ذات قيمة احصائية فى كل مجموعات المرض مقارنة بالمجموعة الضابطة بينما على الجانب الاخر لم يحدث اى زيادة فى نسبة الهيماتوكريت فى كل مجموعات المرض مقارنة بالمجموعة الضابطة ولكن كل من مادة الفيبرينوجين ولزوجة البلازما قد زادت فى المرضى الذين زادت مدة المرض لديهم عن خمس سنوات (مجموعة ١ب ، ١ج) مقارنة بالمجموعة الضابطة وكذلك مقارنة بمجموعة المرضى الذين تقل مدة المرض لديهم عن خمس سنوات بينما انخفض معامل تحور كرات الدم الحمراء فى المرض الذين تزيد مدة المرض لديهم عن خمس سنوات (مجموعة ١أ) مقارنة بالمجموعة الضابطة وكذلك المجموعة التى تقل مدة المرض فيها عن خمس سنوات .

وقد أظهرت هذه الدراسة أيضا تغيرات ذات قيمة احصائية فى الدهون والدهون البروتينية فى مجموعات المرضى مقارنة بالمجموعة الضابطة وقد تمثلت هذه التغيرات فى زيادة كل من الكوليسترول الكلى والبروتين الدهنى منخفض الكثافة وكذلك مادة التراجلسريد بينما حدث انخفاض ذو قيمة إحصائية فى نسبة البروتين الدهنى مرتفع الكثافة فى كل مجموعات المرض (١أ، ١ب ، ١ج) ما عدا مادة الكوليسترول الكلى والتى شهدت ارتفاعا ولكنه غير ذو قيمة احصائية فى مجموعة المرضى الذين تتراوح مدة المرض لديهم ما بين خمسة وعشر سنوات مقارنة بالمجموعة الضابطة .

وكذلك لوحظ وجود تباطأ فى سرعة تدفق الدم سواء قبل حقن مادة الدياموكس أو بعد ١٥ دقيقة من اعطاء هذا العقار وكذلك استجابة هذه الشرايين بعد حقن مادة الدياموكس فى المرضى الذين تزيد مدة المرض لديهم عن خمس سنوات (المجموعة ١ب ، ١ج) مقارنة بالمجموعة الضابطة .

وقد اظهرت هذه الدراسة هذه العلاقات التناسبية:-

١-قد لوحظ وجود تناسبا طرديا بين مدة المرض وكل من نسبة الهيماتوكريت والكوليسترول الكلى والبروتين الدهنى منخفض الكثافة ولزوجة الدم ومادة الفيبرنوجين وكذلك وجد أن مدة المرض تتناسب تناسبا عكسيا مع معامل تحور

ملخص البحث

يعتبر مرض السكر الأكثر شيوعا بين أمراض الغدد الصماء فى الأطفال وقد لوحظ زيادة معدلات الحياة لهؤلاء الأطفال الذين يعانون من مرض البول السكرى المعتمد على الأنسولين نظرا لتحسن ظروف العلاج والتى لوحظ معها زيادة معدلات حدوث مضاعفات ومن اهم هذه المضاعفات التأثير على الأوعية الدموية ولقد أثبتت الدراسات وجود تغييرات فى سيولة الدم فى مرض البول السكرى ومما قد يكون لها دور هام فى حدوث مضاعفات بالاوعية الدموية وخصوصا شرايين المخ .

وقد أجريت هذه الدراسة على ٣٩ من الاطفال والبالغين الذين يعانون من مرض البول السكرى من كلا الجنسين مقارنة بثلاثة عشرة من الاطفال والبالغين الاصحاء فى نفس العمر كمجموعة ضابطة وقد قسمت مجموعة مرض البول السكرى إلى ثلاث مجموعات فرعية الاولى (١أ) وتتكون من ثلاثة عشرة مريض يعانون من مرض البول السكرى لمدة أقل من خمس سنوات والمجموعة الثانية (١ب) وتتكون من نفس العدد وتتراوح مدة المرض لديهم من خمس الى عشرة سنوات والمجموعة الثالثة (١ج) وتتكون من نفس العدد وتزيد مدة المرض لديهم عن عشرة سنوات .

وكل هؤلاء الاطفال والبالغين سواء اكانوا مرضى أو مجموعة ضابطة قد خضعوا للفحص الطبى الدقيق وكذلك قياس سرعة تدفق الدم بالمخ بأستخدام جهاز الدوبلر وقد تم القياس لهم قبل اعطائهم عقار الداياموكس وكذلك بعد خمسة عشرة دقيقة بعد اعطائهم هذا العقار وذلك لقياس مدى استجابة شرايين المخ وتدفق الدم لها بعد اعطاء هذا العقار وقياس مدى مرونة هذه الشراين وكذلك ثم احتساب نسبة الهيماتوكريت وكذلك الهيموجلوبين المسكر وكذلك قياس الدهون والدهون البروتينية بالدم والتى تشمل الكوليسترول الكلى وكذلك البروتين الدهنى عالى الكثافة وكذلك البروتين الدهنى منخفض الكثافة وكذلك مادة التراجلسريد وكذلك ثم قياس لزوجة البلازما وكذلك قدرة كرات الدم الحمراء على التحور وكذلك نسبة الفيبرينوجين بالدم .

بسم الله الرحمن الرحيم

قالوا سبحانك
لا علم لنا إلا ما علمتنا
إنك أنت العليم الحكيم

صدق الله العظيم

سورة البقرة آية (٣٣)